PASS Information

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Research question and objectives	Primary Objectives To assess the relative risk of major and minor congenital malformations at birth and throughout the first year of life – comparing maternal first trimester duloxetine exposure to four comparator groups: 1) Pregnant women not exposed to duloxetine (duloxetine non-exposed); 2) Pregnant women exposed to a Selective Serotonin Reuptake Inhibitor [SSRI] (SSRI exposed); 3) Pregnant women exposed to venlafaxine (venlafaxine exposed); and, 4) Women exposed to duloxetine prior to pregnancy but not during pregnancy (duloxetine discontinuers). Secondary Objectives

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	1) To assess the risk of non-live birth (spontaneous abortions, elective abortions, stillbirths) comparing maternal duloxetine exposure to comparators (duloxetine non-exposed , SSRI exposed, venlafaxine exposed and duloxetine discontinuers). 2) To assess the risk of preterm birth and small for gestational age (SGA) – comparing maternal exposure to duloxetine in early (first 20 weeks of pregnancy) and late (from week 20 of pregnancy and throughout pregnancy) exposure to duloxetine to comparators (duloxetine non-exposed, SSRI exposed, venlafaxine exposed and duloxetine discontinuers).
Country(-ies) of study	Denmark, Sweden
Author	PPD
Signature of principal investigator	Signature on file/see approval date below

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Table of contents

1. Abstract

Title

Observational Study to Assess Fetal Outcomes Following Maternal Exposure to Duloxetine

Keywords

Duloxetine, maternal exposure, drugs in pregnancy, malformation

Rationale and background

Antidepressants are widely used among women of reproductive age and many studies have evaluated possible negative pregnancy outcomes for women in treatment during pregnancy. However, very few studies have analyzed possible associations between duloxetine exposure and potential negative consequences for the developing fetus and the newborn.

Research question and objectives

To assess the safety of maternal exposure to duloxetine during pregnancy for the developing fetus and the newborn. Specifically:

Primary Objectives

To assess the relative risk of major and minor congenital malformations – comparing maternal first trimester duloxetine exposure to four comparator groups:

- Pregnant women not exposed to duloxetine (duloxetine non-exposed);
- Pregnant women exposed to a Selective Serotonin Reuptake Inhibitor [SSRI] (SSRI exposed);
- Pregnant women exposed to venlafaxine (venlafaxine exposed); and,
- Women exposed to duloxetine prior to pregnancy but not during pregnancy (duloxetine discontinuers).

Secondary Objectives

1. To assess the risk of non-live birth (spontaneous abortions, elective abortions, stillbirths) comparing maternal duloxetine exposure to comparators (duloxetine non-exposed, SSRI exposed, venlafaxine exposed, and duloxetine discontinuers).
2. To assess the risk of preterm birth and small for gestational age (SGA) – comparing maternal exposure to duloxetine to comparators (duloxetine non-exposed, SSRI exposed, venlafaxine exposed and duloxetine discontinuers discontinuers).

Study design

This is a register-based cohort study based on nationwide data from Sweden and Denmark. Redeemed prescriptions during time windows relevant for each outcome of interest were used to assess exposure and co-medication. Outcomes of interest were identified by ICD-10 codes given at hospitals or variables registered in the medical birth registers.

Setting, subjects and study size, including dropouts

Exposure to duloxetine between 2004 to 2016 was investigated in a cohort including all registered pregnancies in Sweden and Denmark. The final cohort consisted of more than 2 million pregnancies.

Variables and data sources

Redeemed prescriptions (exposure and co-medication) were available from Danish and Swedish nationwide prescription registers one year before pregnancy, and during pregnancy. ICD-10 codes for women (comorbidity, stillbirths, and abortions) were available five years prior and during pregnancy and ICD-10 codes for offspring (malformations) were available throughout the first year after birth from nationwide hospital registers. Information about pregnancies (last menstrual period (LMP), end of pregnancy, offspring birth weight, smoking during pregnancy, and for a subgroup, body mass index (BMI) was available from nationwide medical birth registers.

Maternal duloxetine exposure was defined as having redeemed a prescription for duloxetine during the relevant time window. Four comparator groups were constructed to analyze the risk of duloxetine and analyze trends and their impact: duloxetine non-exposed, SSRI exposed, venlafaxine exposed , and duloxetine discontinuers.

Logistic regression and Cox proportional hazards models were used to estimate odds ratios and hazard ratios. The estimates are presented unadjusted and adjusted for age, year, income, education, smoking, psychiatric admissions, data-source (Sweden or Denmark), comorbidity and comedication. Also, a propensity score matched analysis was performed.

In addition, sensitivity analyses were performed redefining exposure to two redeemed prescriptions, calculation of exposure periods based on number of pills redeemed for each prescription, inclusion of BMI as a covariate and restricting the cohort to the first pregnancy in the study period. Analyses of abortion (spontaneous and elective) were only performed on data from Denmark.

Results

Table 1.1 shows odds ratios / hazard ratios for the propensity score matched analyses. Statistically significant results ($p<0.05$) are marked in bold.

Table 1.1 Summary of the main results - propensity score matched analyses*

Outcome	Comparators			
	Duloxetine Non-Exposed	SSRI Exposed	Venlafaxine Exposed	Duloxetine discontinuers
Major malformations	0.98 (0.74;1.30)	1.07 (0.78;1.46)	0.95 (0.66;1.36)	0.80 (0.56;1.14)
Minor malformations	1.09 (0.82;1.45)	**1.39 (1.00;1.94)**	1.20 (0.82;1.76)	1.11 (0.77;1.60)
Spontaneous abortions (cox)	1.08 (0.89;1.31)	**1.25 (1.00;1.57)**	1.08 (0.82;1.41)	0.99 (0.76;1.30)
Spontaneous abortions (logistic regression)	1.02 (0.84;1.24)	1.18 (0.95;1.47)	1.10 (0.85;1.42)	0.95 (0.73;1.23)
Elective abortions	**1.41 (1.25;1.59)**	**1.32 (1.15;1.51)**	1.09 (0.93;1.27)	**1.46 (1.23;1.75)**
Stillbirths	0.71 (0.28;1.85)	0.83 (0.29;2.37)	1.00 (0.29;3.45)	1.00 (0.29;3.45)
SGA early exposure	0.83 (0.69;1.01)	0.96 (0.77;1.18)	1.18 (0.91;1.52)	0.96 (0.75;1.23)
SGA late exposure	0.70 (0.47;1.05)	0.57 (0.38;0.87)	1.58 (0.89;2.81)	0.73 (0.45;1.17)
Preterm early exposure	**1.33 (1.10;1.60)**	1.21 (0.99;1.47)	0.91 (0.73;1.14)	1.17 (0.93;1.49)
Preterm late exposure	**1.76 (1.28;2.42)**	**1.79 (1.25;2.56)**	1.26 (0.86;1.86)	**2.04 (1.29;3.23)**

*Estimates are shown as hazard ratios (Spontaneous abortions (cox)) or odds ratios (all other) with 95% confidence intervals. Propensity scores were based on maternal education, age, comorbidity, comedication, hospital contacts (somatic and psychiatric), year of pregnancy and family income. For non-abortion outcomes the propensity score was also based on maternal smoking, previous spontaneous abortion, and stillbirths.

Discussion

Primary Objective: No increased risk of minor or major congenital malformations, including all subtypes, was found. This result is in accordance with previous studies and case-reports analyzing this association.

Secondary Objectives:

- Spontaneous Abortions: An increased risk of spontaneous abortion was found for women exposed to duloxetine compared to women exposed to SSRIs. No increased risk was found when comparing women exposed to duloxetine to women unexposed to duloxetine, exposed to venlafaxine, or duloxetine discontinuers. The sensitivity analyses show differing trends depending on the definition of exposure and choice of cohort. The interpretation of these results is not clear; therefore, the results are inconclusive. An increased risk of spontaneous abortions for women exposed to duloxetine during pregnancy cannot be ruled out. However, this increased risk may be explained by confounding factors (e.g. depression severity) due to the lack of association when comparing women exposed to duloxetine to women discontinuing duloxetine during pregnancy.

- Elective abortion: The association with elective abortions needs to be further analyzed in a setting where additional factors that lead to elective abortions are included. Most of the elective abortions occurred in early pregnancy.
- Stillbirths: No increased risk in stillbirths was found with duloxetine exposure, both in the main and sensitivity analyses. No previous analyses have evaluated the risk of stillbirth for women exposed to duloxetine during pregnancy.
- Small for Gestational Age (SGA): No increased risk of SGA births for duloxetine exposure was found both in the main and sensitivity analyses. This outcome has not previously been analyzed for duloxetine.
- Preterm birth: An increased risk of preterm birth was found for women exposed to duloxetine during pregnancy compared to unexposed women, SSRI exposed and duloxetine discontinuers. There was no increased risk compared to venlafaxine exposure. The increased risk for preterm birth, has previously been well described for other antidepressants (compared to unexposed), but not for duloxetine. When interpreting these results, it has to be taken into consideration that previous studies have found an increased risk of preterm birth for women with depressive disorders during pregnancy not exposed to any antidepressant.

It is reassuring for clinicians and women in treatment with duloxetine that the exposure during pregnancy is not related to minor or major malformations, stillbirths, and SGA. The increased risk of preterm birth and spontaneous abortions needs to be taken into consideration when assessing the risk-benefit balance of drug treatment during pregnancy, where benefits for the mother need to be weighed against risks for the unborn child for each individual case.

Conclusion

Based on this observational register-based nationwide study with data from Denmark and Sweden, no increased risk of congenital major or minor malformations were found for women exposed to duloxetine during the first trimester. Furthermore, no increased risk of stillbirths or SGA births was found.

An increased risk of spontaneous abortions was found but data was inconclusive.

We found an increased risk associated with elective abortions. The available registers do not allow for addressing this outcome in full, and a true association cannot be ruled out, although the results suggested some degree of confounding by indication e.g. depression severity.

The increased risk of preterm birth compared to unexposed, SSRI exposed and duloxetine discontinuers is in accordance with previous studies analyzing other antidepressants. In the present study, an increased risk compared to SSRI exposed, but not venlafaxine exposed was found, suggesting an SNRI class effect.

Women and physicians considering duloxetine treatment during pregnancy are therefore to weigh possible benefits for the mother against risks for the unborn child for each individual case.

Marketing Authorisation Holder(s)

Eli Lilly and Company

Names and affiliations of principal investigators

2. List of abbreviations

Term	Definition
AR	Adverse Reaction
ATC	Anatomical Therapeutic Chemical Classification
BMI	Body Mass Index
CI	Confidence Interval
CRF	Case Report Form
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ERB	Ethical Review Board
HR	Hazard Ratio
ICD-10	International Classification of Diseases 10th revision
LMP	Last Menstrual Period
OR	Odds Ratio
OTC	Over-The-Counter
PASS	Post-Authorization Safety Study
PS	Propensity Score
RR	Relative Risk
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SGA	Small for Gestational Age
SNRI	Serotonin and Norepinephrine Reuptake Inhibitor
SSRI	Selective Serotonin Reuptake Inhibitor

3. Investigators

PPD

PPD

4. Other responsible parties

Not applicable.

5. Milestones

Milestone	Planned date	Actual date	Comments
Start of data collection	30 May 2018	15 October 2018	Data collection prolonged due to new EU legislation (GDPR)
End of data collection	31 December 2018	15 April 2019	Missing variables in received data set (in Sweden)
Registration in the EU PAS register	02 August 2017	02 August 2017	As planned
Final report of study results	28 March 2019	See Page 1	

6. Rationale and background

6.1. Treatment of Depression during Pregnancy

Studies suggest that depression is common during pregnancy and up to 15% of pregnant women suffer from depression or depressive symptoms,(1–4) about 10% develop major depression(5) and up to 13% are treated with medications.(6–9) Use of antidepressants (AD) in pregnant women has grown steadily over time.(6–12) In Denmark, a study reported that between January 1997 and January 2010, the percentage of pregnant women exposed to an antidepressant increased from 0.2% in 1997 to 3.2% in 2009.(9) Selective Serotonin Reuptake Inhibitors (SSRI)s are the most commonly used ADs worldwide and in Denmark and Sweden,(9,10,13) followed by Serotonin and Norepinephrine Reuptake Inhibitors (SNRI)s.(9,14)

Treatment of depression with ADs during pregnancy is indicated for some women to control their symptoms.(15) ADs have been proven to control mood effectively and reduce risks associated with untreated depression for both the mother and her offspring.(16–18) Untreated mood disorders in the mother may have consequences for both the mother and her offspring.(17,19–21) It is speculated, however, that a significant number of pregnant women are not treated for their depression,(22–24) and around 60% of women using an AD before pregnancy do not continue through the first trimester.(9,14,25)

In addition, depression and anxiety may increase the risk for obstetric complications, puerperal pathologies and impaired fetal and postnatal development including gestational hypertension and subsequent preeclampsia, bleeding, prematurity, and Small for Gestational Age (SGA).(24,26,26–44) (45) However, since most studies did not assess the potential independent effect of medications,(29,42) it remained unclear whether such associations are due to biologic or behavioral factors intrinsic to women with mood disorders, to medications used to treat the disorder, or a combination of both. Furthermore, women with a diagnosis of a major depressive disorder are more likely to smoke or intake alcohol or other substances, which may confound the association between depression and pregnancy outcomes.(43,44)

6.2. Safety of Antidepressants in Pregnant Women

There has been concerns about the safety of ADs use during pregnancy. In some studies, first trimester exposure to certain SSRIs has been associated with specific birth defects,(46–50) while SSRI use late in pregnancy has been associated with pulmonary hypertension of the newborn,(51) prematurity,(51–53) low birth weight,(52,53) SGA,(54) and various neonatal complications.(52,53,55,56) However, other studies have not found these associations.(57–63) Again, since most studies did not assess the potential independent effects of medications and depression severity, it has been unclear to what extent such associations are due to biologic or behavioral factors with high prevalence in women with mood disorders (such as smoking, substance abuse, or poor diet), to medications used to treat the disorder, or a combination of

both. It is of note, that for some outcomes, such as pulmonary hypertension of the newborn, studies demonstrated that the increase risk initially suggested is modest (OR 1.51 (95% CI, 1.35-1.69)) and the absolute risk (0.3%) is small.(64) These small absolute risk increases need to be taken into consideration when evaluating the clinical impact of treatment during pregnancy. Although the relative risk might be increased, the absolute risk remains small. Data regarding the safety of SNRIs during pregnancy is sparse. Therefore, this study is proposed to focus on evaluating the association between maternal exposure to one specific SNRI, duloxetine, during pregnancy and the risk of the following pregnancy outcomes: Major and minor congenital malformations, preterm birth, SGA, stillbirths, spontaneous and elective abortions. These outcomes have been associated with other ADs, in the literature (see sections below).

6.2.1. Major Congenital Malformations

One of the most concerning adverse effects of medications during pregnancy is teratogenicity. In Denmark and Sweden, approximately 3% of all infants are born with serious birth defects.(63) Deaths due to birth defects are one of the leading causes of infant mortality. Recent evidence on this topic has clearly demonstrated the impact of confounding by the underlying indication of depression using a variety of different methodological approaches: Restriction of the cohort to women with a depression diagnosis,(65) sibling controlled analyses,(66) and comparison between pregnancies with exposure to SSRIs during the first trimester versus pregnancies with paused SSRI treatment.(63) Evidence for non-SSRI ADs is scarce. In general, studies have found no association between SNRIs and major malformations; but they were based on small exposed cohorts.(67,68) In contrast to the single-action antidepressants SSRIs, SNRIs (e.g. duloxetine) are dual-action, affecting not only serotonin, but also norepinephrine levels in the brain.(69) This different mode of action could be associated with a different safety profile, which calls for further studies.

6.2.2. Preterm Birth and Small for Gestational Age (SGA)

These outcomes are leading causes of maternal and/or perinatal mortality and morbidity.(70–72) Low birth weight can be the result of prematurity or of fetal growth retardation or restriction. Preterm birth (< 37 weeks of gestation) accounts for approximately 10% of all births and is the leading cause of perinatal deaths(70) and long term disabilities.(70) Infants with growth restriction are born smaller than their peers with the same gestational age at birth. Based on the distribution of birth weights within levels of gestational age, a newborn with a birth weight below the 10^{th} percentile is considered SGA. Infants SGA may have a term or preterm birth. However, a preterm infant is not necessarily born SGA. Infants SGA are also at a greater risk of death and are more likely to develop diabetes, cardiovascular disease, schizophrenia and other serious conditions.(70,71) Maternal use of SSRIs during pregnancy has been associated with prematurity,(52,53,55,73) low birth weight,(52,53) and SGA.(52,58) However, evidence is

conflicting.(74) Both SSRIs and SNRIs affect serotonin levels and can therefore, in theory, be expected to be associated with the same side effects. This might be the reason why some studies have also reported an increased risk of prematurity and SGA in patients treated with non-SSRI ADs.(52,55) On the other hand, as previously mentioned, there are concerns about the potential adverse effects of depression itself. Psychological conditions such as stress, anxiety and depression may elevate the risk of these outcomes through increased activity of the hypothalamo-pituitary-adrenal axis and release of corticotropin-releasing hormone or other vasoactive hormones and neuroendocrine transmitters.(32,75,76) Whether these risks extend to SNRIs remains unclear.

6.2.3. Spontaneous and elective abortions

Since Bassiouni and Rafei showed that women who experienced spontaneous abortion had a higher concentration of serotonin in the blood compared with women giving birth, there has been a great concern regarding treatment with SSRIs, and other ADs impacting the serotonergic system.(77) Although several studies have investigated the risk of miscarriage for pregnant women in treatment with SSRIs, the results are contradictory(73,78–84) and only a few studies have addressed a potential confounding by indication.(85) SNRIs have not been studied for a possible association with abortions, and there is a need for studies addressing the issue.

The association between exposure to duloxetine and elective abortions has not previously been analyzed.

6.2.4. Stillbirths

As mentioned above, studies have investigated a possible association between AD exposure and spontaneous abortions, congenital malformations and other pregnancy outcomes. Some of these conditions and malformations are potentially fatal in utero, but information on the risk of stillbirth for children has primarily been limited to SSRIs.(86,87) Knowledge on risks associated with exposure to SNRIs, like duloxetine, is very limited and needed. Furthermore, large cohorts are needed to assess the risk of this rare outcome, with an incidence of 0.3-0.4% in Denmark and Sweden.(88)

6.3. Duloxetine

Duloxetine is a selective SNRI approved in the United States and Europe in 2004. It is currently indicated for the treatment of major depressive disorder, generalized anxiety disorder, stress urinary incontinence and diabetic peripheral neuropathic pain in Europe. These conditions are common among women of childbearing age.(89) Information from post-marketing surveillance systems suggests a similar pattern of adverse pregnancy outcomes in women using duloxetine

during pregnancy compared to the general population.(90)(91,92) One uncontrolled pregnancy register including 168 live births prenatally exposed to duloxetine reported 3 major malformations (1.8%), which was considered within the expected baseline range in that population.(93) One study based on the Swedish Birth Register identified 286 live-born infants exposed to duloxetine in the first trimester, seven were born with malformations (relative risk of 0.8; 95% CI 0.32–1.64 compared to non-exposed).(94) In addition, symptoms in the newborn characterized by jitteriness, poor muscle tone, weak cry, respiratory distress, hypoglycemia, low Apgar score, and seizures have been reported after in utero exposure. (95) On the other hand, two similar cases reported no signs of withdrawal syndrome.(96,97)

A recent review concluded that the evidence for duloxetine is limited but does not suggest a clinically important increased risk of major congenital malformations.(98) However, there are no published large controlled studies examining the safety of duloxetine in pregnancy.

A Danish register based study showed an increased risk of spontaneous abortions associated with use of duloxetine during pregnancy (unadjusted RR 2.12; 95% CI 1.52–2.96);(84), however, the results were not adjusted for confounders and the sample size was small. Importantly, the statistical analyses did not take time-to-event analysis into consideration, in contrast to other studies analyzing the same outcome.(85) Given the limitations of spontaneous adverse reports and the small sample size of the register, additional information is needed to support conclusions about the safety of duloxetine. Moreover, there is no robustly designed study on the risk of other adverse outcomes such as preterm birth, SGA, or non-live births (spontaneous, elective abortions and stillbirths).

7. Research question and objectives

The objective of this study is to provide a systematic evaluation on the safety of duloxetine in pregnant women. Therefore, the risk of fetal outcomes in relation to duloxetine in a population-based cohort of pregnant women redeeming a prescription for duloxetine, before or during pregnancy, will be quantified. The relative risk of adverse events in pregnancies exposed during etiologically relevant periods relative to a cohort of women with similar underlying disease, but not treated with duloxetine, will be estimated.

The study objectives are as follows:

To assess the safety of duloxetine for the *developing fetus and the newborn*. Specifically:

Primary Objectives

To assess the relative risk of major and minor congenital malformations at birth and throughout the first year of life – comparing maternal first trimester duloxetine exposure to four comparator groups:

- Pregnant women not exposed to duloxetine (duloxetine non-exposed);
- Pregnant women exposed to a Selective Serotonin Reuptake Inhibitor [SSRI] (SSRI exposed);
- Pregnant women exposed to venlafaxine (venlafaxine exposed); and,
- Women exposed to duloxetine prior to pregnancy but not during pregnancy (duloxetine discontinuers).

Secondary Objectives

1. To assess the risk of non-live birth (spontaneous abortions, elective abortions, stillbirths) comparing maternal duloxetine exposure to comparators (duloxetine non-exposed , SSRI exposed, venlafaxine exposed and duloxetine discontinuers).
2. To assess the risk of preterm birth and small for gestational age (SGA) – comparing maternal exposure to duloxetine in early (first 20 weeks of pregnancy) and late (from week 20 of pregnancy and throughout pregnancy) exposure to duloxetine to comparators (duloxetine non-exposed, SSRI exposed, venlafaxine exposed and duloxetine discontinuers).

8. Amendments and updates

Not applicable.

9. Research methods

9.1. Study design

The study is a retrospective observational study based on nationwide registers from Denmark and Sweden. All pregnancies, in the two countries, ending in elective abortion, spontaneous abortions or birth, and their offspring are included in the cohort. Due to the birth registers' high completeness, over 99% of all live births and stillbirths are included in the cohort.(99–102) The study period is between 2004 and 2016. Due to the unique personal identification number given to all citizens, it was possible to link the cohort with other registers relevant for the analyses. In the registers, the personal identification number is encrypted, whereby individuals could not be identified.

Maternal exposure to duloxetine, or other medications, are defined as a redeemed prescription for duloxetine at a community pharmacy, during the etiologically relevant time period.

The primary study outcome is

- Major and minor malformations

Secondary outcomes are

- Spontaneous abortions, elective abortions
- Stillbirth
- Preterm birth
- Small for gestational age (SGA)

Information on these outcomes was gathered from the national birth registers and national hospital registers, where diagnoses and procedures for inpatients and outpatients are recorded.

Gestational age is recorded in the birth registers and is based on the date of the last menstrual period (LMP) and/or ultrasound estimates.

Four comparison groups were chosen:

1. Women not exposed to duloxetine during the defined time-period
2. Women exposed to SSRIs
3. Women exposed to another SNRI; venlafaxine
4. Women exposed to duloxetine before, but not during pregnancy, to account for possible confounding by indication

9.1.1. Rationale for the design and data source

Non-interventional, observational studies are a cornerstone in studying the associations between drug exposure during pregnancy and negative birth outcomes. Before authorization, a

medication's efficacy and adverse effects are identified in clinical trials where pregnant women often are excluded. The knowledge of medications' influence on pregnant women and their offspring are therefore almost solely based on post marketing observational studies after the medication has been on the market for a considerable amount of time. For these studies, health care utilization databases, such as the national health registers, are often relied on. They provide prospectively collected information for whole nations and allow the study of multiple outcomes. Inclusion of whole nations reduces the risk of selection bias and gives the studies high generalizability. Furthermore, the large sizes of these datasets have, in theory, the potential to generate enough statistical power to examine rare outcomes (e.g. stillbirth) and important subgroups (e.g. duloxetine users).

While studies emerging from these databases lack the benefits of randomization, if carefully designed, the results have been shown to be valid and informative, particularly when evaluating unintended drug effects.

The national health registers comprise a unique cohort for the study of pregnant women in Europe, due to the registers' size, quality and long follow-up time. They have been widely used in observational studies dealing with drugs' possible effect on the offspring. There are some limitations of registers that need to be taken into consideration. These are discussed in section Limitations of the research methods 11.2.

9.2. Setting

9.2.1. Study Population

The basis for all the analyses is data from Denmark and Sweden's national birth registers and National Patient Registers. Data in the national birth registers is captured in relation to the pregnant women's contact with health care professionals (physicians, midwifes and others) during and immediately after pregnancy. The National Patient Registers hold data on all procedures and diagnoses given in relation to contacts with a hospital, including abortions. For further details on data sources see Section 9.5.

The final cohorts used for the analyses are either based on pregnancies ending with births in Sweden and Denmark (outcomes: malformation, stillbirth, SGA and preterm birth) or pregnancies ending with abortion or birth in Denmark (outcomes: abortion). Below are the inclusion and exclusion criteria for the population used for analyses of malformation, abortion, stillbirth, SGA and preterm birth, respectively, shown.

9.2.1.1. Major and minor congenital malformations

Inclusion and exclusion criteria for the analyses of major and minor malformation are the same.

Inclusion criteria:

1. Base cohort to include all pregnancies ending in a live birth from the Danish and Swedish national birth registers with linked offspring from 2004 to 2016
2. Information on mother available 12 months prior to the LMP until one month post-delivery, e.g. mothers who are not immigrated this period
3. Information on offspring available up to 12 months after the delivery, e.g. children of mothers who are not immigrated 12 months after delivery

Exclusion criteria:

1. Pregnancies with a chromosomal abnormality based on at least one inpatient or outpatient diagnosis (identified in the patient records registered as a either an A or B diagnosis) of Q87.1, Q87.4, Q9X (International Classification of Diseases 10th revision (ICD-10)) between date of birth and date of birth+365days
2. Pregnancies complicated by outpatient exposure to definite teratogens (Warfarin [ATC: B01AA03], antineoplastic agents [ATC: L01], isotretinoin [ATC: D10AD04, D10BA01, D10AD54], misoprostol [ATC: A02BB01, G02AD06, M01AE56], lithium [ATC: N05AN, N05AN01] and thalidomide [ATC: L04AX02]) from LMP through LMP plus 90 days (i.e., days of exposure overlap with 1st trimester)
3. Pregnancies in which duloxetine is dispensed in the 3 months (LMP–90days) prior to the LMP but not during the first trimester (to ensure that there is no misclassification of the non-exposed), except for the analyses using these duloxetine discontinuers as the reference group

9.2.1.2. Spontaneous abortions and elective abortions

For the analyses of abortions only data from Denmark is used. Data from Sweden was not included in these analyses because information on elective abortions and date of spontaneous abortion is not available in the national register. Data from Denmark has previously been used to estimate risk of abortion among duloxetine exposed pregnant women.(84) The study only included data from 1997 till 2008. Inclusion and exclusion criteria are similar for the analyses of spontaneous abortions and the analyses of elective abortions.

Inclusion criteria:

1. Base cohort to include all pregnancies (ending in either stillbirth or live birth) from the Danish national birth registers with linked offspring and all women with a diagnosis of abortion (either elective or spontaneous) from the Danish national hospital registers, from 2004 to 2016
2. Information on mother available 12 months prior to the LMP until one-month post-delivery/abortion, e.g. mothers who have not been immigrating this period. Hereby, to gain information about redeemed prescriptions.

Exclusion criteria:

1. Missing information on gestational length or date of abortion

9.2.1.3. Stillbirths

Inclusion criteria:

1. Base cohort to include all pregnancies ending in birth (either stillbirths or live birth) from the Danish and Swedish national birth registers with linked offspring from 2004 to 2016
2. Information on mother available 3 months prior to the LMP until delivery, e.g. mothers who are not immigrated this period

Exclusion criteria:

1. Pregnancies for which information on gestational age is missing or implausible (before week 20 or after week 45)

9.2.1.4. Preterm birth and small for gestation age (SGA)

Inclusion and exclusion criteria are similar for the analyses of preterm birth and the analyses of SGA.

Inclusion criteria:

1. Base cohort will include pregnancies ending in a live birth from the Danish and Swedish national birth registers with linked offspring from 2004 to 2016
2. Information on mother available 12 months prior to the LMP until one month post-delivery, e.g. mothers who are not immigrated this period
3. Information on the offspring for month 1 after the delivery is required, e.g. mother is not emigrated during the first month after delivery

Exclusion criteria:

1. Pregnancies for which information on gestational age is missing or implausible (before week 20 or after week 45)
2. Offspring where information on birth weight is missing
3. Pregnancies in which duloxetine is dispensed between 3 months prior to the LMP until start of the exposure period (to ensure that there is no misclassification of the non-exposed), except for the analyses using these duloxetine discontinuers as the reference group

9.3. Subjects

In this study, the population consisted of all pregnancies registered in the Medical Birth Register and all spontaneous and elective abortions in the National Patient Register, in Denmark and Sweden. For specific data sources and validity see Section 9.5.

For the propensity score (PS) analyses matching was performed as described in Section 9.9.2.

9.4. Variables

9.4.1. Outcomes

9.4.1.1. Major congenital malformation

Major congenital malformation was defined as a record of an ICD-10 diagnosis from Q00-Q99 according to the EUROCAT classification of major congenital malformations version 1.4. (103) All diagnoses within the first year of life or until death were included.

Major malformations were identified by ICD-10 codes in the National Hospital Registers as either an A or B diagnosis between date of birth and date of birth+365 days. Major malformations were defined as the following ICD-10 codes: Q-chapter, D215, D821, D1810, P350, P351, P371, except the ICD-10 codes used to define minor malformations.

9.4.1.2. Minor Congenital Malformations

The ICD-10 records were used to define minor malformations according to the EUROCAT classification of major congenital malformations version 1.4.

Minor malformation is identified in the National Hospital Registers as a either an A or B diagnosis between date of birth and date of birth+365 days. Minor malformation is defined as the ICD-10 codes listed in Table 9.1.

Table 9.1 ICD-10 codes used to identify minor malformation

EUROCAT Classifications	ICD-10 code
Compression facies	Q671
Depressions in skull	Q6740
Dolichocephaly	Q672
Dysmorphic face	Q189
Facial asymmetry	Q670
Plagiocephaly – head asymmetry	Q673
Macrocephalus	Q753
Other congenital deformities of skull, face and jaw	Q674
Blue sclera	Q135
Congenital ectropion	Q101
Congenital entropion	Q102
Crocodile tears	Q0782
Hypertelorism	Q752
Other congenital malformations of eyelid	Q103
Stenosis or stricture of lacrimal duct	Q105
Synophrys	Q1880
Accessory auricle, preauricular appendage, tag, or lobule	Q170
Asymmetric size	Q173

Bat ear, prominent ear	Q175
Double lobule	Q170
Lack of helical fold	Q173
Low set ears	Q174
Macrotia	Q171
Microtia	Q172
Posterior angulation	Q173
Preauricular sinus or cyst	Q181
Primitive shape	Q173
Protuberant ears	Q173
Unspecified and minor malformation of ear	Q179
Deviation of nasal septum	Q6741
Dysmorphic nose	Q189
High arched palate	Q3850
Macrocheilia	Q186
Macroglossia	Q382
Macrostomia	Q184
Microcheilia	Q187
Microstomia	Q185
Retrognathia	Q674
Tongue tie or cyst of tongue	Q381
Congenital malformation of face and neck, unspecified	Q189
Other branchial cleft malformations	Q182
Preauricular sinus or cyst	Q181
Sinus, fistula or cyst of branchial	Q180
Torticollis	Q680
Accessory carpal bones	Q7400
Clinodactyly (5th finger)	Q6810
Enlarged or hypertrophic nails	Q845
Single/abnormal palmar crease	Q8280
Clicking hip subluxation or unstable hip	Q653
Clicking hip subluxation or unstable hip	Q654
Clicking hip subluxation or unstable hip	Q655
Clicking hip subluxation or unstable hip	Q656
Clubfoot of postural origin – other congenital deformities of feet	Q668
Congenital deformity of feet, unspecified	Q669
Congenital pes planus	Q665
Enlarged or hypertrophic nails	Q845
Hallux varus – other congenital varus deformities of feet	Q663
Metatarsus varus – other congenital valgus deformities of feet	Q666
Metatarsus varus or metatarsus adductus	Q662

Pes cavus	Q667
Talipes or pes calcaneovalgus	Q664
Accessory nipples	Q833
Mongoloid spot (whites)	Q8252
Neavus flammeus	Q8250
Pigmented naevus – congenital non-neoplastic naevus	Q825
Strawberry naevus	Q8251
Absence of rib	Q7660
Accessory rib	Q7662
Cervical rib	Q765
Congenital bowing of femur	Q683
Congenital bowing of fibula and tibia	Q684
Congenital bowing of long bones of leg, unspecified	Q685
Congenital deformity of spine	Q675
Congenital lordosis, postural	Q7643
Depressed sternum	Q676
Genu recurvatum	Q6821
Prominent sternum	Q677
Shield-like chest, other congenital deformities of chest	Q678
Spina bifida occulta	Q760
Sternum bifidum	Q7671
Single congenital cerebral cyst	Q0461
Absence or hypoplasia of umbilical artery, single umbilical artery	Q270
Patent ductus arteriosus, if GA <37 weeks	Q250
Patent or persistent foramen ovale	Q2111
Peripheral pulmonary artery stenosis, if GA < 37 weeks	Q256
Persistent left superior vena cava	Q261
Persistent right aortic arch	Q2541
Accessory lobe of lung	Q331
Azygos lobe of lung	Q3310
Congenital laryngeal stridor	Q314
Laryngomalacia	Q314
Laryngomalacia	Q315
Tracheomalacia	Q320
Functional gastro-intestinal disorders	Q4021
Functional gastro-intestinal disorders	Q4320
Functional gastro-intestinal disorders	Q4381
Functional gastro-intestinal disorders	Q4382
Hiatus hernia	Q401
Meckel's diverticulum	Q430
Pyloric stenosis	Q400

Hyperplastic and giant kidney	Q633
Single renal cyst	Q610
Vesico-ureteral-renal reflux	Q627
Bifid scrotum	Q5521
Congenital malformation of vulva	Q527
Fusion of labia	Q525
Hymen imperforatum	Q523
Retractile testis	Q5520
Undescended testicle	Q53
Congenital malformation, unspecified	Q899
Balanced translocations or inversions in normal individuals	Q950
Balanced translocations or inversions in normal individuals	Q951

9.4.1.3. Spontaneous and elective abortions

Abortions were defined as a record of an ICD-10 diagnosis gathered from the National Hospital Registers:

All registered cases of spontaneous abortions were identified by the following codes: O021 and O03 according to the ICD-10.

All records of elective abortion according to ICD-10 codes O04, O05 and O06.

If gestational age was above 22 weeks for spontaneous abortions, these were recoded as stillbirths.

9.4.1.4. Stillbirth

Information on stillbirth was gathered from the Medical Birth Registers and defined as a child birth showing no signs of life at birth. For Danish data, spontaneous abortions after week 22 was defined as stillbirths. The method by which data on perinatal mortality are recorded has been described previously.(104)

9.4.1.5. Preterm birth

Information on preterm birth was gathered from the Medical Birth Registers and defined as a live birth between the 20^{th} and 37^{th} week of gestation.

9.4.1.6. Small for gestational age (SGA)

SGA was defined as fetuses with growth restrictions that are born smaller than their peers with the same gestational age at birth.

SGA was defined as children with a birth weight under the 10^{th} percentiles in samples stratified on pregnancy week, sex and country.

9.4.1.7. Major malformation subtype

Subtypes of major malformations were identified as an ICD-10 code in the National Hospital Registers as either an A (primary) or B (secondary) diagnosis between date of birth and date of birth+365 days. Specific major malformations were defined as specified in Table 9.2.

Table 9.2 ICD-10 codes used to identify specific major malformations

Major malformation Subtype	ICD-10	Note
Nervous system	Q00, Q01, Q02, Q03, Q04, Q05, Q06, Q07	
Eye	Q10, Q11, Q12, Q13, Q14, Q15	
Ear, face and neck	Q16, Q17, Q18	
Congenital Heart Defects	Q20, Q21, Q22, Q23, Q24, Q25, Q26	Exclude Q250 or Q256 with gestational age <37 weeks
Respiratory	Q300, Q32, Q33, Q34	Exclude Q336
Oro facial clefts	Q35, Q36, Q37	Exclude Q000 or Q042
Digestive system	Q38, Q39, Q40, Q41, Q42, Q43, Q44, Q45, Q790	
Abdominal wall defects	Q792, Q793, Q795	
Urinary	Q61, Q62, Q63, Q64, Q794	
Genital	Q50, Q51, Q52, Q54, Q55, Q56	
Limb	Q65, Q66, Q67, Q68, Q69, Q70, Q71, Q72, Q73, Q74	
Other anomalies	Q7402, Q77, Q7800, Q782, Q783, Q784, Q785, Q786, Q787, Q788, Q750, Q7980, Q893, Q894, Q80, Q81, Q82, Q8726, Q0435, Q411, Q412, Q418, Q710, Q712, Q713, Q720, Q722, Q723, Q730, Q793, Q795, Q7980, Q206, Q240, Q3381, Q890, Q893, Q86, Q860, Q8680, P350, P351, P371, Q4471, Q6190, Q7484, Q7484, Q751, Q754, Q7581, Q87, Q936, D830	

9.4.2. Exposures

For the medicinal product exposures all products were administered orally, and there was no available information on the specific dose or duration of treatment prescribed by the physician. In the sensitivity analyses, the number of redeemed pills and their strengths to estimate treatment length based on defined daily doses has been used. See Section 9.9.4.

Maternal exposure to duloxetine, or other medications, were defined as redemption of a prescription at a community pharmacy, during the etiologically relevant time period. Data were gathered from the national prescription register in both countries. Table 9.3 shows the medications included in the study and their ATC codes.

Table 9.3 Drugs used to define exposure and comparison groups, and their ATC codes

Medication	ATC code
Antidepressants	N06A
SSRIs	N06AB
Duloxetine	N06AX21
Venlafaxine	N06AX16

9.4.2.1. Major and minor congenital malformations

Exposure definition

Redeemed prescription of duloxetine during the first trimester (LMP to LMP+90 days).

Comparison group definition

- Duloxetine non-exposed: No redeemed prescription of duloxetine during the first trimester (LMP to LMP+90 days)
- Venlafaxine exposed: Redeemed prescription of venlafaxine and no redeemed prescription of duloxetine during the first trimester (LMP to LMP+90 days)
- SSRI exposed: Redeemed prescription of an SSRI and no redeemed prescription of duloxetine during the first trimester (LMP to LMP+90 days)
- Duloxetine discontinuers: Women with redeemed prescription of duloxetine one year prior to pregnancy (LMP-365 days to LMP), but no redeemed prescription of duloxetine during the first trimester (LMP to LMP+90 days)

9.4.2.2. Abortions

Similar exposure and comparison group definitions in the analyses of elective and spontaneous abortions.

Exposure definition

Redeemed prescription of duloxetine during the first 20 weeks of pregnancy (LMP-30 days to LMP+140 days) .

Comparison groups definitions

- Duloxetine non-exposed: No redeemed prescription of duloxetine during the first 20 week of pregnancy (LMP-30 days to LMP+140) Venlafaxine exposed: Redeemed prescription of venlafaxine and no redeemed prescription of duloxetine during the first 20 week of pregnancy (LMP-30 days to LMP+140)
- SSRI exposed: Redeemed prescription of an SSRI and no redeemed prescription of duloxetine during the first 20 week of pregnancy (LMP-30 days to LMP+140)
- Duloxetine discontinuers : Women with a least one redeemed prescription of duloxetine one year prior to pregnancy (LMP-365 days to LMP), but no redeemed prescription of duloxetine during the first 20 week of pregnancy (LMP-30 days to LMP+140).

9.4.2.3. Stillbirths

Exposure definition

Redeemed prescription of duloxetine during pregnancy (between LMP to delivery date).

Comparison groups definitions

- Duloxetine non-exposed: Women without a redeemed prescription of duloxetine during pregnancy (LMP to delivery date)
- Venlafaxine exposed: Redeemed prescription of venlafaxine and no redeemed prescription of duloxetine during pregnancy (LMP to delivery date)
- SSRI exposed: Redeemed prescription of an SSRI and no redeemed prescription of duloxetine during pregnancy (LMP to delivery date)
- Duloxetine discontinuers: Women with a least one redeemed prescription of duloxetine one year prior to pregnancy (LMP-365 days to LMP), but no redeemed prescription of duloxetine during pregnancy (LMP to delivery date)

9.4.2.4. Preterm birth and small for gestational age (SGA)

Exposure and comparison group definitions are similar in the analyses of preterm birth and SGA:

Exposure definition

- Early exposure: Redeemed prescription of duloxetine early in pregnancy (LMP to LMP+140 days)
- Late exposure: Redeemed prescription of duloxetine late in pregnancy (LMP+141 days to date of delivery)

Comparison group definitions

- Duloxetine non-exposed:
  - Early exposure: No redeemed prescription of duloxetine early in pregnancy (LMP to LMP+140 days)
  - Late exposure: No redeemed prescription of duloxetine late in pregnancy (LMP+141 days to date of delivery)
- Venlafaxine exposed:
  - Early exposure: Redeemed prescription of venlafaxine and no redeemed prescription of duloxetine early in pregnancy (LMP to LMP+140 days)
  - Late exposure: Redeemed prescription of venlafaxine and no redeemed prescription of duloxetine late in pregnancy (LMP+141 days to date of delivery)
- SSRI exposed:
  - Early exposure: Redeemed prescription of SSRI and no redeemed prescription of duloxetine early in pregnancy (LMP to LMP+140 days)
  - Late exposure: Redeemed prescription of SSRI and no redeemed prescription of duloxetine late in pregnancy (LMP+141 days to date of delivery)
- Duloxetine discontinuers:
  - Early exposure: Women with redeemed prescription of duloxetine one year prior to pregnancy (LMP- 365 days to LMP), but no redeemed prescription of duloxetine early in pregnancy (LMP to LMP+140 days)
  - Late exposure: Women with redeemed prescription of duloxetine one year prior to pregnancy (LMP- 365 days to LMP), but no redeemed prescription of duloxetine late in pregnancy (LMP+141 days to date of delivery)

9.4.3. Potential confounders

To account for potential confounders, analyses were adjusted for the following covariates: Country of residence, birth year of the newborn, maternal age, number of previous spontaneous abortions, birth order, smoking, comedication, comorbidity and socioeconomic status (income and education). For specific variables see Table 9.11.

The underlying indications for treatment with duloxetine were expected to be important confounders, either due to a direct effect of the conditions or due to lifestyle or other factors associated with the conditions. Since information on indication for treatment is not available, diagnoses within 5 years of pregnancy was used as proxies for indication. It was also attempted to account for the severity of the underlying indications (e.g., depression) through the use of surrogate measures (co-prescribed medications and measures of healthcare use intensity such as the number of psychiatric admissions). It is believed that more use of other psychiatric medication, and visits to psychiatric wards is associated with depression severity. These measures are, however, proxies for depression severity, and the available data does not allow for fully adjustment of severity which could lead to some residual confounding. Other important potential confounders include chronic comorbid conditions (on the assumption that those with a higher burden of comorbid illness may be more likely to use an antidepressant) including for example diabetes, hypertension, and renal disease. These were measured directly using ICD-10 diagnosis given in connection to hospital contacts. In addition, exposure (redemption of a prescription) to medications used as treatment for these conditions (e.g., antihypertensive medications, insulin, oral diabetes medications) was used as proxies for the diagnosis in the statistical models. Patients with these "common" conditions are seldom treated at a hospital, and therefore hospital diagnoses are underreported. Therefore, diagnoses with appropriate drug redemptions was supplemented. Patient demographic characteristics, if they are associated with treatment and outcome, may also be important confounders and were accounted for in the analyses.

The use of medications up to a one-year period before pregnancy and during pregnancy, which may be markers for the presence or the severity of comorbid illness, were assessed. For the analysis of congenital malformations, the use of suspected teratogenic medications during the first trimester was also assessed.

A greater disparity in baseline characteristics before adjustment indicated a higher likelihood for unmeasured confounding factors to play a role in the association. If unmeasured confounders are associated with the analyzed outcome, it could result in a falsely increased risk associated with the exposure. Balance in characteristics after propensity score (PS) matching indicated a lower risk of confounding by measured characteristics. However, unmeasured confounders may still have biased the estimate, particularly if not associated with the measured characteristics.

In Table 9.4, known or suspected risk factors for the study outcomes that are either unmeasured or poorly measured are presented. These factors were unlikely to be important confounders for the planned analyses. To bias the results, the risk factor would need to be imbalanced between the duloxetine exposed and comparison group, within the levels of the measured covariates included in the PS. The most concerning as potential sources of residual confounding in the planned analyses are alcohol use and drug abuse. The other unmeasured or poorly measured risk factors are not recognized determinants of treatment with an SNRI, making this scenario unlikely. However, to address the potential for residual confounding by these and other factors

not accounted for by measured covariates, comparator groups (in addition to a non-exposed comparator) were used in the analyses. The comparator groups that are more likely to resemble the duloxetine user group included women exposed to venlafaxine, SSRIs, and duloxetine discontinuers. Confounding by indication is a term used when a variable is a risk factor for a disease among non-exposed persons and is associated with the exposure of interest in the population from which the cases derive, without being an intermediate step in the causal pathway between the exposure and the disease. If depression is causally linked to any of the outcomes studied (as some studies have suggested), the risk estimate of use of duloxetine in pregnancy (primarily used in the treatment of depression) could thereby be falsely increased.

Table 9.4 Risk factors for study outcome that are unmeasured or poorly measured in the Danish and Swedish Registers

Congenital malformations	Preterm birth	Small for gestational age
• Obesity; • Infections: Toxoplasmosis; Rubella; Cytomegalovirus; Herpes; Syphilis; Varicella; Parvovirus B19; Zika virus; Lymphocytic choriomeningitis virus (LCMV); Influenza; • Physical and environmental agents: Lead; Ionizing radiation; Fever/ hyperthermia; Fish consumption related methylmercury exposure • Family history • Alcohol use	• Life events (divorce, separation, death) • Occupational risk factors • Uterine anomaly, including diethylstilbestrol-induced changes in uterus and leiomyomas • History of second-trimester abortion • History of cervical surgery • Sexually transmitted infections • Bacteriuria • Periodontal disease • Vaginal bleeding, especially in more than one trimester • Previous preterm birth • Substance abuse	• Fetal infection • Confined placental mosaicism • Family history • Assisted reproductive technologies • Low pre-pregnancy weight • Poor gestational weight gain • Malabsorption • Malnutrition • Residing at high altitude • Short interpregnancy interval

Congenital malformations	Preterm birth	Small for gestational age
	• Poor nutrition and low body mass index (BMI) • Family history of preterm birth, especially maternal first-degree family history of spontaneous preterm birth, particularly if the pregnant woman herself was born preterm • Environmental factors	

9.5. Data sources

9.5.1. The Health System in Denmark and Sweden(105)

In Denmark and Sweden, about 80% of the health care funding comes from public sources. County or regional councils provide most of the health care services. Capitation in combination with service fees is used for all Danish general practitioners, while various fee-for-service systems are used in Sweden.

In Denmark, elective abortion is legal and freely available for pregnant women until the end of gestational age week 12. If the woman is pregnant longer than week 12, elective abortion can still be performed, if, among other things, the pregnancy entails a degradation of the woman's health (somatic or mental), the women is incapable of giving proper care to a child due to somatic or mental health status or of there is a risk of birth defects to the fetus.(106,107)

All Nordic countries had global hospital budgeting in the 1980s; since then other systems, predominantly combinations of diagnosis-related group financing and global budgets have been implemented. The amounts of resources devoted to health care are about the same in Denmark and Sweden whether measured by the proportion of gross domestic product devoted to health care, or by hospital beds or doctor/patient ratios. In monetary terms, Denmark spends more than Sweden. Despite similar amounts of resources, they are used quite differently across the countries. Differences of a factor of two or more are observed for pharmaceuticals. Despite all these differences, the health care systems are quite similar when seen in a global perspective.

Denmark and Sweden offer excellent opportunities to assess long term effects to exposure during fetal life. Through the 10- or 11-digit code assigned to each citizen, included in the national

registers, it is possible to link information from different registers and thereby follow each individual from the beginning of life until death. The national registers, which are constructed in a similar way and with similar contents, have been used for numerous studies and contributed to important scientific works. Rare exposures and rare outcomes demand very large databases and as both Denmark and Sweden are small countries with a population ranging from 5.7 million to 10 million, respectively; the data in each country are probably too sparse to evaluate associations between specific drugs and specific malformations or other rare outcomes.

A large dataset can be accomplished by combining information from the health registers in the two countries. Women planning a pregnancy and their physicians are entitled to get as reliable information as possible concerning risks with medication that can be used during pregnancy and this can only be achieved through rich data sets combined with high quality studies.

9.5.2. Prescription data

Denmark and Sweden have a nationwide prescription database containing electronically submitted information on prescriptions dispensed by pharmacies.(108–110) In total across the Nordic countries, the databases cover the countries' 26.6 million inhabitants (16 million for Denmark and Sweden). Data from the autonomic regions of the Faroe Islands and Greenland are not included in the Danish data. The data collected are determined by country-specific regulations, but all include information on the prescriptions together with information from different administrative registers. Data are transferred electronically monthly from pharmacies to the prescription database. According to the legislation, no informed consent is required for collection of the prescription data, but individuals may see information about themselves if they make an enquiry. When the register data are used for research purposes, the possible findings cannot be used for decisions concerning individual patients. The national prescription databases in Denmark and Sweden cannot be used for supervision of either individual patients or prescribers. These registers include both purchased prescription of reimbursed drugs and not reimbursed drugs.

All individuals/patients included in the prescription databases have a unique personal identifier based on their person identification number, permitting linkage between various population-based data sources. Some prescription databases routinely include the date of death and migration, while others need to be linked to this information. Regarding drug exposure, the article number is a unique identifier for each drug formulation of a medicinal product used in the Nordic countries. This number constitutes the link to other registers providing detailed information on dispensed drugs. The drugs are classified according to the global ATC system. Numbers of WHO's defined daily doses dispensed are recorded, as well as the number of packages and the reimbursement code. There are several challenges in using these data. Firstly, the reimbursement system differs between the two countries. Secondly, the indication for the prescription is not yet fully recorded in the databases. The dispensing (redemption) date and

retail price are included in all the registers, but the prescription date is at present not included in the Danish prescription databases.

The majority of sales of non-prescription over-the-counter (OTC) medicines are not in the prescription databases. Only OTC medicines prescribed and dispensed to individual patients, e.g. for obtaining reimbursement in chronic diseases, are included. The indication for use and the prescribed dose is to some extent included, but only as free text and thus not easily available for research purposes. Furthermore, the validity of indications has not yet been validated. Patient level data on drug use in hospitals and other institutions are not available for the present study period. None of the registers have complete data on vaccines.

9.5.3. The Medical Birth Registers

Denmark and Sweden have kept medical birth registers for decades, all with compulsory notification.(111,112) All livebirths as well as stillbirths from varying gestational ages in the different countries are notified to the registers. All registers contain basic information on the mother, the neonate and the father as well. Linkage to other registers and national databases using the personal identity numbers can provide additional data on diseases and medical conditions of the mother, the father and the neonate, as well as on social conditions, education, prescribed medications, and social security/insurance data. Thus, it is possible to conduct longitudinal and intergenerational studies and even in some instances include information on relatives and offspring within the period of registration.

Diagnoses are registered as ICD-10 codes. The international origin of the codes for some main groups created through the registers allows for cross-country research on large populations within the countries. However, codes for each individual case are assigned on national platforms and this may involve minor differences between the countries. Birth notification forms are linked to or part of the system and thus to population census offices.

9.5.4. National Hospital Registers

Information on some of the chosen outcomes (Section 9.4.1) will be gathered from the national hospital registers.(113,114) They include discharge diagnoses of all patients in contact with a hospital. Personal 10- or 11-digit number allows linkage of information from different registers whereby each individual and their diagnoses can be followed up from the beginning of life until death. Table 9.5 summarizes the two registers.

Table 9.5 Brief Description of the National Hospital Registers Included in the Study and Their Variables of Interest

Register	Year of Establishment	Brief Description	Sample Variables of Interest Available for This Study
The Danish National Patient Register(113)	1977	Information on all patients in contact with a Danish hospital.	Discharge diagnoses and their date.
National Inpatient Register (IPR) (Sweden) (114)	1964	Information on all completed in- and out-patient admissions at public hospitals.	Hospital admission and discharge, diagnoses, surgery, including dates.

9.5.5. Validity

Systematic validation of data is essential for the credibility of register-based research. Validation of variables for specific studies has been carried out in all registers, but they cover different periods and have only been applied to selected conditions. Overall these validation studies have found the registers valid with only few missing values.

The specific outcomes regarding this study have primarily been validated in the Danish registers, probably since Denmark was the first country to allow the use of administrative health registers in research. Several studies have validated the quality of different diagnoses. In general more than 99% of all hospital contacts are registered in the Danish National Hospital Register, specifically, more than 99% of all births are recorded in the National Danish Medical Birth Register.(115) The quality of the malformation diagnoses has been validated and found to have a predictive value of 88% for having a congenital malformation, with a completeness of 90%. Any misclassification of the diagnoses is most probably random, and not attributable to a specific drug exposure.(101) Diagnoses of heart defects have been validated in another study and have been found to have a positive predictive value of 98.4.(116) Furthermore, in Denmark the diagnosis of spontaneous abortions has been validated and found to have a positive predictive value of 97.4.(100) If women experience a miscarriage without recognizing it or do not contact a doctor the number of registered miscarriages will be underestimated. This underreporting has been estimated to be 30% and is probably due to miscarriages early in pregnancy.(117) The date of abortion is always included, but the gestational length is missing in a very limited number of cases.

The definition of preterm (<37 weeks of gestation) is based on the mothers reported date of LMP, and two subsequent ultrasounds in the first and second trimester. This data is recorded by the midwife in the Medical Birth Registry and in the National Hospital Registry as an ICD-10 code. The coding of gestational age has not been validated, but there is no reason to believe that gestational age is not valid or recorded differently based on the mother's drug exposure.

The validity of the information on stillbirths has not been estimated, but since it is statutory by law to register stillbirths, it is believed that the information is of high quality and completeness.

There is no reason to believe that the validity of the different outcome variables should have a different level of validity in Sweden.

9.5.6. Education and income data

All Nordic countries have high quality education and income data on each citizen in the country. (118–127) Registers that all have been used for research purposes several times before, are based on national statistics on education and tax reports. Not all educations are comparable and therefore an adjusted variable on educational length was made and used as a proxy for level of education. Income data was categorized in quartiles within calendar year. See Section 9.8, data transformation, for further details.

9.5.7. Overview of data sources

Table 9.6 Description of data sources and their respective variables of interest used in the present study

Name of register	Description	Variables of interest
Denmark		
The Danish National Patient Register (113)	Information on all patients in contact with a Danish hospital.	Discharge diagnoses and their date.
The Danish National Prescription Register (108,109)	Contains information on the total redemption of prescriptions in Denmark at community pharmacies since 1994. Data is held by Statistics Denmark.	Date, type, strength and quantity of drug dispensed.
Medical Birth Register (128)	Registration is to monitor the health of the newborns and of the quality of the antenatal and delivery care services.	Mothers´ age, parity, BMI and smoking. Offspring's time of gestation and conception.
The Danish Civil Registration System (129,130)	Information on all Danish citizens, including date of	Date of death or emigration

	death, immigration or emigration.	
The Danish Education Register (131)	Information on education, level and length on all people educated in Denmark or immigrated to Denmark.	Education level and length
The Danish register on personal income and transfer payments(122)	Information on income and tax payment, earned income, pensions and benefits.	Household income before tax
Sweden		
National Patient Register (114)	Information on all completed in- and out-patient admissions at public hospitals.	Hospital admission and discharge, diagnoses, surgery, incl. dates. Diagnoses of malformations and comorbidity.
The Swedish Prescribed Drug Register (110)	Contains information on the total redemption of prescriptions in Sweden since 2005.	Date, type, strength and quantity of drug dispensed.
Swedish Medical Birth Register (111)	Contains data on practically all deliveries in Sweden. The register's key data contains information about prenatal care, delivery care and neonatal care.	Infant diagnoses, smoking etc.
The Swedish Population Register (132)	Information on all Swedish citizens, including date of death, immigration or emigration.	Date of death or emigration
The Swedish Register of Education (133)	Information on education, level and length on all people educated in Sweden or immigrated to Sweden.	Education level and length
The Swedish Income Register (134)	Information on income and tax payment, earned income, pensions and benefits.	Household income before tax

9.5.8. Quality Assurance and Quality Control

All aspects of data analysis were conducted according to standard procedures of the Research Group of Drugs in Pregnancy and Copenhagen Phase IV Unit (Phase4CPH) at Center for Clinical Research and Prevention, Copenhagen University Hospital. Validation of the programming has been performed. Smaller programs (3-20 lines of coding) have been reviewed by an independent statistical programmer, longer programs have been recoded by and independent statistical programmer.

9.5.9. Study Time Frame and Lag Time Issues

Data from the registers for all outcomes including abortions covered the period from 2004 to 2016.

9.6. Bias

Observational register-based studies, due to their nature, have bias that can affect the assessment of the results, which will be discussed in the following. Although several efforts have been undertaken to account for possible bias related to the present study, there will remain some biases that cannot be addressed or accounted for. These possible biases must be taken into consideration when interpreting the results of the present study.

Due to the nationwide coverage of the included registers from Denmark and Sweden and their high validity and completeness (see Section 9.5) the risk of selection bias (sampling bias, allocation bias and lost to follow up bias) is minimal. This can, however, limit the external validity. It is, however, believed that the results have a high external validity in a Nordic country setting. The authors are confident that the results are applicable to other western European countries with free and universal healthcare, since treatment regimens are comparable.

Treatment regimens are also comparable to the U.S. where indications and treatment guidelines are similar to the studied population. It is not believed that the characteristics of women using duloxetine during pregnancy differ substantially between the Nordic countries and the U.S., and therefore the results might be applicable in a U.S. setting as well.

All data was collected prospectively and there is therefore no risk of recall bias.

There is a risk of detection bias in the analyses concerning congenital malformations. In theory, women exposed to duloxetine and their offspring visit their physician more often than non-exposed women, which may lead to an increased probability of detecting malformations within the first year. This is especially relevant for less severe heart defects (e.g. atrium septum defects) that often are not detected at birth.

Diagnoses are only recorded in the registers in relation to a hospital contact, both as an inpatient or as an outpatient. Hence, diagnoses given by general practitioners are not included in the registers. There is therefore a probability of underestimating the rate of diagnoses treated outside

the hospital setting e.g. hypertension, diabetes, mild infections, migraine and mild /moderate pain. Some of these diagnoses are, however, accounted for indirectly by assessing drug redemptions for these conditions.

The main challenge in register-based studies concerning drug exposure is confounding by indication. This possible bias is addressed in Section 9.6.1.

9.6.1. Confounding

In the present study, cohorts from two different countries were used to address possible confounders related to a country's health care system and guidelines.

All analyses were adjusted for available confounders, being covariates that are believed to be related to antidepressant exposure (age, parity, year, comorbidity, co-medication), or are proxies for factors related to being exposed to an antidepressant (education, income, smoking, BMI, co-medication, comorbidity) as well as the respective study outcomes.

Due to the fact that confounding by indication cannot be totally accounted for, we were not able to fully compare women exposed to duloxetine during pregnancy to women with the same characteristics but not in treatment with duloxetine. This would require a randomized controlled trial, which is impossible due to ethical considerations. The present study strives to address confounding by indication by constructing four comparator groups. These groups are expected to provide information regarding confounding:

a) women not exposed to duloxetine during the relevant exposure window;
b) women exposed to SSRIs, to analyze factors related to being exposed to an antidepressant (active comparator group).
c) women exposed to venlafaxine, to analyze factors related to being exposed to an antidepressant in the same class (SNRI) as duloxetine (active comparator group).
d) women exposed to duloxetine before LMP, but not during pregnancy, to analyze factors related to being exposed to duloxetine. These women have previously had an indication for duloxetine and therefore expected to resemble women exposed to duloxetine during pregnancy on other parameters than exposure.

Comparisons groups b) and c) are active comparator groups: SSRIs, other SNRIs (Venlafaxine)

Unmeasured confounders related to the indication and their magnitude might differ depending on the studied outcome. Some unmeasured confounders like e.g. cervix insufficiency will be related to preterm birth, but unlikely related to malformations. Their magnitude will depend on their association strength with the studied outcome. Confounders that are time dependent will differ for e.g. congenital malformation where exposure window is the first trimester, and preterm birth where the exposure window is the whole pregnancy. Reduced intake of e.g. folic acid will probably be stronger associated with neural tube defects, than elective abortions.

Furthermore, PS-matching was performed to make the comparison groups as comparable as possible based on available covariates (see Section 9.9.2)

Lastly, four sensitivity analyses for all exposures and outcomes were performed:

1. Redefinition of exposure to having redeemed >1 prescription for duloxetine during the relevant time window with reference groups SSRI, and venlafaxine to require > 1 prescription. This was done to account for possible misclassification of exposure, as it is theorized that redeeming at least 2 prescription during the relevant time window increases the probability of exposure.
2. Redefinition of exposure to cover days' supply that overlaps with the relevant time window. The exposure will be calculated based on the number of redeemed pills and their strength compared to the WHO's daily defined dose. This was done to account for possible misclassification of exposure, as it is theorized that women redeeming prescriptions outside the relevant time window might still be exposed. This applies especially for women redeeming prescriptions less frequently.
3. Restriction of the cohort to the first pregnancy occurring within the study period. These analyses were performed to account for possible relation between pregnancies for the same individual.
4. Inclusion of body mass index (BMI) in the statistical model as a covariate for pregnancies where information on BMI is available. High BMI is known to increase the risk of negative pregnancy outcomes and is a proxy for life factors not included in the available registers for the present study.

9.7. Study size

9.7.1. Pre-specified power calculation

According to Statistics Denmark (SD) and the Swedish National Board of Health and Welfare the prevalence of duloxetine exposure was 0.5% (mean prevalence between 2006 and 2015 for Denmark and Sweden), among women of fertile age (20-39 years old). It is assumed that the prevalence was similar for pregnant women, where approximately 60% do not continue treatment throughout the first trimester, and therefore it was calculated that approximately 3,000 patients exposed to duloxetine during the first trimester were projected in Sweden and Denmark during the study period. The frequency of exposure decreases during pregnancy such that approximately 500 to 1000 exposed during the "late pregnancy" exposure window was projected. It was estimated that the power to detect significant differences (alpha=0.05, 2-sided) at various numbers of exposed women and levels of relative risk for outcomes assuming a prevalence in the non-exposed of 15% (e.g. elective abortion),(85) 10% (e.g., preterm birth, SGA, spontaneous abortions),(85,135) 3% (e.g. major malformations), 1% (e.g., cardiac malformations),(63) 0.5% (e.g. stillbirths) and 0.1% (e.g., rare malformations).(63) The background population were all pregnancies not exposed to duloxetine. Matching was performed for the PS matched analyses. A 1:4 ratio of matching (cases: controls) was sought but had to be reduced for some comparison groups due to the low number of available controls. Given that the number of exposed in the cohort was 3,000 the study would have 99% power to detect relative

risk difference of 1.5 for the primary study outcome, major malformation. The background risk of major malformations is 3%. Power to detect associations based on the number exposed and relative risks are shown in Table 9.7.

Table 9.7 Power to detect associations based on the number exposed and relative risks

	RR					RR				
Exposed	**1.25**	**1.5**	**2**	**3**	**5**	**1.25**	**1.5**	**2**	**3**	**5**
	RISK IN NON-EXPOSED: 10%*					RISK IN NON-EXPOSED: 3%**				
150	0.16	0.44	0.90	1.00	1.00	0.08	0.18	0.46	0.87	1.00
300	0.27	0.70	0.99	1.00	1.00	0.12	0.29	0.70	0.99	1.00
450	0.36	0.85	1.00	1.00	1.00	0.15	0.39	0.84	1.00	1.00
600	0.45	0.93	1.00	1.00	1.00	0.18	0.48	0.92	1.00	1.00
750	0.53	0.97	1.00	1.00	1.00	0.20	0.55	0.96	1.00	1.00
900	0.60	0.99	1.00	1.00	1.00	0.23	0.62	0.98	1.00	1.00
1,050	0.67	0.99	1.00	1.00	1.00	0.26	0.68	0.99	1.00	1.00
1,200	0.72	1.00	1.00	1.00	1.00	0.29	0.74	1.00	1.00	1.00
1,350	0.77	1.00	1.00	1.00	1.00	0.32	0.78	1.00	1.00	1.00
1,500	0.81	1.00	1.00	1.00	1.00	0.34	0.82	1.00	1.00	1.00
3,000	0.95	1.00	1.00	1.00	1.00	0.67	0.99	1.00	1.00	1.00
	RISK IN NON-EXPOSED: 1%***					RISK IN NON-EXPOSED: 0.1%****				
150	0.06	0.10	0.22	0.50	0.87	0.04	0.06	0.09	0.15	0.26
300	0.07	0.14	0.34	0.73	0.99	0.04	0.06	0.11	0.20	0.38
450	0.08	0.18	0.45	0.86	1.00	0.05	0.07	0.13	0.24	0.48
600	0.09	0.22	0.54	0.93	1.00	0.05	0.08	0.14	0.29	0.57
750	0.11	0.25	0.62	0.97	1.00	0.05	0.08	0.16	0.32	0.64
900	0.12	0.29	0.69	0.99	1.00	0.05	0.09	0.17	0.36	0.71
1,050	0.13	0.32	0.74	0.99	1.00	0.05	0.09	0.18	0.40	0.76
1,200	0.14	0.35	0.79	1.00	1.00	0.06	0.10	0.20	0.43	0.80
1,350	0.15	0.38	0.83	1.00	1.00	0.06	0.10	0.21	0.46	0.84

1,500	0.15	0.41	0.86	1.00	1.00	0.06	0.10	0.22	0.49	0.87
3,000	0,28	0.78	1.00	1.00	1.00	0.06	0.13	0.41	0.93	1.00

* This assumes 10% risk among non-exposed

** This assumes 3% risk among non-exposed

*** This assumes 1% risk among non-exposed

**** This assumes 0.1% risk among non-exposed

The study ended up comprising 1,516 women exposed to duloxetine during the first trimester. The post-hoc power calculation shows a 82% power to detect relative risk difference of 1.5 for the primary study outcome, major malformations.

9.8. Data transformation

Household income: Disposable household income was available for the years 2004-2016 in Swedish data, and 2003-2017 in Danish data. Income in the year of LMP was identified, except for Swedish women with LMP in 2003, who got information from 2004. If information was not available for the given year, first it was imputed one year prior to LMP, and if still missing, income was imputed from 1 year after LMP, where possible. Income was grouped in quartiles, stratified on year and country[1]. This was to account for difference in salary level between Sweden and Denmark, inflation during the study period and possible differences in the way variables are calculated in Sweden and Denmark.

Age of mother at time of LMP was available. Age was grouped as 18-24, 25-29, 30-34, >34 years. In the Statistical Analysis Plan (SAP) the age group was defined as <20 and 20-24, however, because of the low number of women being <20 years of age when getting pregnant, the two groups where combined to one group of women 18-24 years of age.

Table 9.8. ICD-10, ATC codes and time periods used to identify comorbidity.

Comorbidity	ICD10 code	Time period for ICD10 code	ATC code	Time period for ATC code
Diabetes	E10, E11, E12, E13, E14	5 year prior to LMP	A10AB01, A10AB04, A10AB05, A10AB06, A10AC01, A10AD01, A10AD04, A10AD05, A10AD06, A10AE04, A10AE05, A10AE06, A10BA02, A10BB01,	1 year prior to LMP

[1] This is a deviation from the study protocol, where standardization for 2015-year level was proposed. However, when grouping in quartiles stratified on year, the standardization is not needed.

			A10BB03, A10BB07, A10BB09, A10BB12, A10BD07, A10BD08, A10BD09, A10BD10, A10BD11, A10BD13, A10BD15, A10BD16, A10BD20, A10BF, A10BG03, A10BH01, A10BH02, A10BH03, A10BH04, A10BH05, A10BX02, A10BX04, A10BX07, A10BX09, A10BX10, A10BX11, A10BX12, A10BX14,	
Diabetes during pregnancy	O24	5 year prior to LMP		
Hyper and hypothyroidism	E05	5 year prior to LMP	H03AA01, H03BA02, H03BB01, H03BB02, H03CA	1 year prior to LMP
Hypertension	I10, I11, I12, I13, I15	5 year prior to LMP		
Obesity	E66	5 year prior to LMP	A08AB01, A08AA03	1 year prior to LMP
Renal failure	N17, N18, N19	5 year prior to LMP		
Depression	F32, F320, F321, F322, F323, F328, F329, F33, F330, F331, F333, F334, F338, F339	5 year prior to LMP		
Affective	F34, F340, F341, F348, F349, F38, F380, F381, F388, F39	5 year prior to LMP		
Anxiety, phobia, OCD	F400, F401, F402, F410, F411, F42	5 year prior to LMP		
Severe stress reaction	F430, F431, F432	5 year prior to LMP		
Stress urinary incontinence	DN393	5 year prior to LMP		

Diabetic peripheral neuropathic pain	E114, E104	5 year prior to LMP		

Comorbidity: Prespecified comorbidities were identified through National Patient Registers up to five years prior to LMP, except from gestational diabetes, identified as diagnosis registered during the index pregnancy. See Table 9.8 for ICD-10 and ATC codes. The available registers only include diagnoses for patients in contact with a hospital (see Section 9.5.4). Some diseases are less frequently treated at hospitals (e.g. diabetes and hyper or hypothyroidism). For these diagnoses, redemption of relevant ATC codes was used as proxy for the diseases, in addition to the diagnosis. Comorbidities extended with redeemed prescriptions of relevant drugs up to one year prior to LMP were: Hyper or Hypothyroidism, diabetes and obesity.[2] See Table 9.9 for ATC codes used.[3]

Co-medication: All co-medication is identified by redeemed prescriptions from 90 days prior to LMP and to the end of the relevant time window for each outcome. See Table 9.9 for a list of included medications, and their ATC codes, used to identify co-medication.[4] Women were exposed if they had 1 redeemed prescription.

Table 9.9 ATC codes used to define comedication

Medication	ATC
Antiepileptics	N03
Antihypertensive	C02, C03, C07, C08, C09
Antipsychotics	N05A
Antithyroid	H03B
Anxiolytics	N05B
Betamethasone	H02AB01
Budesonide	A07EA06
Cortisone	A01AC03, A07EA02, C05AA01, H02AA02, H02AB09, H02AB10, S01BA03
Danazol	G03XA01
Dexamethasone	A01AC02, H02AB02
Estradiol	G03AA01, G03AA02, G03AA03, G03AA04, G03AA05, G03AA06, G03AA07, G03AA08, G03AA09, G03AA10, G03AA11, G03AA12, G03AA13, G03AA14, G03AA15, G03AA16,

[2]Development of the "Chronic Condition Measurement Guide" - a new tool to measure chronic conditions in older people based on ICD-10 and ATC-codes. Juul-Larsen HG, Christensen LD, Andersen O, Bandholm T, Kaae S, Petersen J. European Geriatric Medicine (Online April 10, 2019)

[3] The use of ATC codes to identify comorbidity is a deviation from the study protocol. The reason for expanding the definition of comorbidity to include ATC codes is to identify more women with the given comorbidities when combining ATC codes with diagnoses.

[4] Please note, that this is a deviation from the study protocol where co-medication was defined as 1-year prior to LMP. The reason for changing this is that we want information about co-medication during the relevant time window as this is more likely to affect the give outcome, as compared to information on drug exposure 1 year prior to pregnancy.

	G03AB01, G03AB02, G03AB03, G03AB04, G03AB05, G03AB06, G03AB07, G03AB08, G03CA01, G03CA03, G03CA53, L02AA03, V09IX11
Fluconazole	D01AC15, J01RA07, J02AC01
Fluticasone	R01AD08
Glucose lowering	A10
Hydroxyprogesterone	G03DA03, G03FA02, G03AC06, G03DA02, G03FA12, G03FB06, L02AB02
Methimazole	H03BB02
Mometasone	D07AC13, R01AD09, R03BA07
NSAID	M01A
Opioids	N02A
Prednisolone	A07EA01, C05AA04, H02AB04, H02AB06, H02BX01
Prednisone	H02AB07, H02AB15
Progesterone	G03DA04, G03FA04, G03XB
Propylthiouracil	H03BA02
Thyroid	H03A
Triamcinolone	A01AC01, C05AA12, H02AB08
Triptans	N02CC

Moreover, to gain power and because of very sparse number of cells, some of the co-medication was grouped for both the adjusted analyses and the models for the PS:

- A covariate coded yes/no covering steroid hormone exposure was created and covered use of triamcinolone, dexamethasone, cortisone, prednisolone, budesonide, mometasone, betamethasone, prednisone and fluticasone
- A covariate coded yes/no covering progesterone exposure was created and covered use of medroxyprogesterone, progesterone, hydroxyprogesterone
- A covariate coded yes/no covering thyroid hormone exposure was created and covered use of antithyroid, propylthiouracil and methimazole

Smoking: For women registered in the National Medical Birth Register, smoking during pregnancy is available. In order to harmonize data between Sweden and Denmark smoking was coded as a binary variable (yes/no).

Education: Highest completed education was available for the years 2004-2016 in Swedish data, and 2003-2017 in Danish data. Highest completed education in the year prior to the LMP was identified. If information on education was not available, it was imputed one-year post LMP where possible. To be able to harmonize data from Sweden and Denmark, highest completed education was recalculated to years of education and grouped in three categories: <11 years, 11-15 years and >15 years of education.

Previous stillbirths: Women who have a diagnose code for stillbirth (DP95) registered in the National Patient Register before the LMP were identified. Also, in Swedish data the National Medical Birth Register was used to identify women with a previous stillbirth. Because of very few stillbirths the variable was coded as 0, 1+.

Previous spontaneous abortions: Were identified in the National Medical Birth Registers, and grouped as 0,1, 2+.

Birth order: Was identified in the National Medical Birth Register, and grouped as 0,1,2,3+.

Year of birth of the newborn: Was identified in the National Medical Birth Register. To gain power this was grouped in three categories: 2004-2008, 2009-2012, 2013-2016.

Hospital admissions: Number of hospitalizations in the year before pregnancy, both psychiatric and somatic (medical and surgical) were identified in National Patient Registers and grouped in three categories: 0, 1, 2+.

Outpatient courses: Number of outpatient courses during one year before pregnancy, both psychiatric and somatic (medical and surgical) were identified in the National Patient Registers and grouped as 0, 1, 2+.

Emergency department visits: Number of Emergency visits during one year before pregnancy, both somatic and psychiatric, was identified in the Danish National Patient Register and grouped as 0, 1, 2+. This was not possible in Swedish data, due to lack of data on emergency department visits.

Psychiatric hospitalizations: Number of psychiatric hospitalization one year before pregnancy was identified in the National Patient Registers and grouped as 0, 1+.

Psychiatric outpatient visits: Number of psychiatric outpatient courses one year before pregnancy was identified in the National Patient Registers and grouped as 0, 1+.

BMI: For a subgroup of women, BMI was registered in the National Medical Birth Register. BMI was grouped as <21, 21-25, 26-30 and >30 kg/m^2.

9.9. Statistical methods

9.9.1. Main summary measures

Table 9.10 describes the statistical models and measures used to summarize data for each of the prespecified outcomes.

Table 9.10 Overview of models and summary measures given for each of the outcomes

Outcome	*Statistical model*	*Summary measure used for relative risk*	*Summary measure for absolute risk*
Major malformation	Logistic regression	Odds ratio (95% confidence interval)	Events/N (%) for each exposure group
Minor malformation	Logistic regression	Odds ratio (95% confidence interval)	Events/N (%) for each exposure group
Spontaneous abortion	Cox regression	Hazard ratio (95% confidence interval)	Events/N (%) for each exposure group
Elective abortion	Cox regression	Hazard ratio (95% confidence interval)	Events/N (%) for each exposure group
Stillbirth	Logistic regression	Odds ratio (95% confidence interval)	Events/N (%) for each exposure group
Small for gestational age	Logistic regression	Odds ratio (95% confidence interval)	Events/N (%) for each exposure group
Preterm birth	Logistic regression	Odds ratio (95% confidence interval)	Events/N (%) for each exposure group
Subtypes of major malformation	Logistic regression	Odds ratio (95% confidence interval)	Events/N (%) for each exposure group

Unadjusted, adjusted and PS matched analyses were performed for all outcomes. However, for analyses with less than 30 outcome events in the exposed group, only unadjusted and propensity score matched analyses were performed because of lack of power. For all outcomes, the duloxetine exposed women are compared with four different control groups: duloxetine non-exposed, SSRI exposed, venlafaxine exposed and duloxetine discontinuers. Duloxetine exposed were compared with each comparator separately.

9.9.2. Main statistical methods

An overview of the statistical models used to study the different outcomes of interest is given in Table 9.10. For major, minor and subtypes of malformations, a logistic regression was used to investigate the possible elevated risk of exposure of duloxetine compared to the four control groups, respectively. Thus, the analyses of malformation were not done as a time-to-event model. Events of malformation were collected within the first year of the child's life in the present study but were analyzed as present at date of birth. This is reasonably since the malformation is congenital, although not diagnosed up to 12 months after birth. Risk of stillbirth was also analyzed using logistic regression model, as it was not expected that time to stillbirth

has clinical importance in this study. SGA was analyzed by logistic regression since birth weight itself was not of interest, but rather children small for the given gestational age was of interest coded as an indicator variable (yes/no). Preterm birth was analyzed using logistic regression instead of survival analysis on gestational age as it was not expected that the assumption on proportional hazards to be valid as it is of high risk both to be born preterm and substantially post-term. Finally, for analyses of elective and spontaneous abortions, time to events was modelled using the Cox proportional hazard model. Cox regression was used instead of logistic regression to be able to censor persons at time of elective abortion when analyzing spontaneous abortion as outcome and vice versa. Observational time in the analyses of spontaneous abortions was until week 22, as abortions hereafter are seen as stillbirths. Such limitation of observational time is not applied in the analyses of elective abortions[5].

For all outcomes, the duloxetine exposed women are compared with four different control groups: Duloxetine non-exposed, SSRI exposed, venlafaxine exposed and duloxetine discontinuers, see description in Section 9.4.2. For each analysis, three different models were fitted; 1) An unadjusted model to study the association not accounting for any possible confounders and to be able to see how much the associations were influenced by confounders. 2) An adjusted model to be able to see the association adjusted for possible confounders. 3) A PS matched model to see the association adjusted for possible confounders and ensure that groups are as similar as possible before comparison.

The PSs were estimated using a logistic regression and Greedy matching was performed using the SAS macro OneToManyMTCH (Performing a 1:N Case-Control Match on Propensity Score, Lori S. Parsons, Ovation Research Group, Seattle, Washington. Paper 165-29, SUGI 29) with an extension that secures that women are only matched if the difference in PS on the logit scale is a maximum of 0.2 logit(PS). When matching duloxetine exposed with duloxetine non-exposed, a 1:4 ratio was used. Because of limited data in the other control groups, duloxetine exposed were matched with SSRI exposed in a 1:2 ratio, with venlafaxine exposed in a 1:1 ratio, and with duloxetine discontinuers in a 1:1 ratio. If no match was found, duloxetine exposed individuals were not included in the PS matched analyses. In the PS matched dataset, a conditional logistic regression, including the matched group id as a strata variable, was fitted for the analyses of malformation, stillbirth, SGA and preterm birth, respectively. For elective and spontaneous abortions, a stratified Cox proportional hazard regression was fitted stratifying on matching group id.

To assess the balance of possible confounders between matched exposed and each of the comparison groups, standardized differences were calculated using the SAS® macro stddiff macro (*A unified approach to measuring the effect size between two groups using SAS® , Dongsheng Yang and Jarrod E. Dalton, Paper 335-2012, SAS global forum*[6]), which for continuous variables uses standardized mean difference, the standardized risk difference for dichotomous variables and a multivariate Mahalanobis distance for categorical variables with

[5] This is a deviation from the SAP According to SAP the outcome window for elective abortion should be until week 20 However, this is changed to end-of-pregnancy, since elective abortions can occur throughout pregnancy

[6] https://support sas com/resources/papers/proceedings12/335-2012 pdf

more than two levels (*Dalton, J.E. (2008) A new standardized difference metric for multinomial samples*).

For the adjusted analysis models and the PS models, a set of prespecified covariates was given for all main analyses. See Table 9.11. These were preselected based on literature and knowledge on available data. Subsequently, when fitting each model individually, covariates were removed, if the model could not be estimated or covariates were not identifiable in the models, meaning that the parameter estimates were very extreme. All other covariates were kept in the model.

All analyses were performed using SAS Enterprise Guide 7.15 and a significance level at 5% was applied.

Table 9.11 Prespecified sets of confounders for each outcome in the study

Outcome	Potential confounders
Malformation	Data source (Sweden/Denmark), age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, smoking, previous spontaneous abortion, previous stillbirth, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, renal failure, depression, affective disorder, anxiety or phobia, severe stress reaction, stress urinary incontinence, diabetic peripheral neuropathic pain in, glucose lowering, antihypertensive, fluconazole, estradiol, danazol, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination), progesterone (combination), antithyroid (combination);
Stillbirth	Data source (Sweden/Denmark), age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, smoking, previous spontaneous abortion, previous stillbirth, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, renal failure, depression, affective disorder, anxiety or phobia, severe stress reaction, stress urinary incontinence, diabetic peripheral neuropathic pain in, glucose lowering, antihypertensive, fluconazole, estradiol, danazol, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination), progesterone (combination), antithyroid (combination);
Abortion	Age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, renal failure, depression, affective disorder, anxiety or phobia, severe stress reaction, glucose lowering, antihypertensive, fluconazole, estradiol, danazol thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics,

	corticosteroid (combination), progesterone (combination), antithyroid (combination)
Small for gestational age (SGA) and preterm	Data source (Sweden/Denmark), age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, smoking, previous spontaneous abortion, previous stillbirth, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, depression, affective, anxiety or phobia, severe stress reaction, stress urinary incontinence, diabetic peripheral neuropathic pain in, glucose lowering, antihypertensive, fluconazole, estradiol, danazol, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination), progesterone (combination), antithyroid (combination);

9.9.3. Missing values

In general, there are very few missing values in the Danish and Swedish national registers. Diagnose and ATC codes are only registered if the women have a specific diagnose or prescription redeemed. If a certain ICD-10 code is not registered for a woman, the woman is coded as not having the disease. Hospital payments in Denmark depend on registration of diagnoses, therefore there is a high sensitivity on diagnose coding. For a description of completeness of the national registers see Section 9.5, Data Sources.

Information on income and education is gathered from other national registers and is coded as missing for some women. If information on income was not available for the year of LMP, it was imputed one years prior to LMP, and if still missing, income was imputed from 1 year after LMP. If information on education was not available at the year of LMP, it was attempted to be imputed one-year post to LMP.

Missing values for BMI have been identified in the National Medical Birth Registers. This is the reason why the protocol prespecified not to include BMI in the adjustment nor in the model for PS. To investigate the influence of excluding BMI from the analyses, sensitivity analyses were performed where BMI were included in the models and restricted to women with no missing values for BMI.

Data were analyzed under the assumption of missing at random and therefore persons with missing values for some of the variables were deleted from the analyses. In general, a small number of excluded persons due to missing values were found, e.g. for the unadjusted analyses for malformation comparing with non-exposed there were 2,077,206 pregnancies included in the analyses, whereas in the analyses adjusted for covariates included 1,967,290 pregnancies corresponding to 5% of the patients being deleted due to missing values. See Section 4.4, table S4 in the Supplementary material for missing values for specific variables.

9.9.4. Sensitivity analyses

For all analyses, four prespecified sensitivity analyses were performed

1. To study the influence of misclassification, exposure to duloxetine was redefined to having redeemed >1 prescription during the relevant time window . In these analyses, the control groups (SSRI, venlafaxine and duloxetine discontinuers) were also redefined to require > 1 prescriptions.
2. To take into account that some women may be exposed to duloxetine even though they did not redeem a prescription during pregnancy, exposure was redefined as women with overlap between the relevant time window and days' supply of redeemed prescriptions. Days' supply was calculated based on the number of redeemed pills and their strength compared to the WHO's daily defined dose.
3. Events in a woman's first pregnancy may influence the following pregnancies. Therefore, a sensitivity analysis restricting the cohort to the first pregnancy occurring within the study period was performed.
4. A substantial number of women had a missing value for BMI; therefore, the main analyses were not adjusted for BMI. As a sensitivity analysis, women with data on BMI were included adjusting for BMI in the adjusted analyses and including BMI in the PS model.

Statistical methods used in the sensitivity analyses are the same as for the main analyses.

9.9.5. Amendments to the statistical analysis plan

In the protocol, all analyses of SGA (both early and late exposure) were stratified on malformation. However, due to very few events for some of the outcomes among the late exposed, analyses not stratifying on malformation were also performed.

In the protocol, the analyses of spontaneous abortions were specified as Cox regressions. In addition to performing these, analyses of spontaneous abortions were also performed as logistic regressions.

9.10. Quality Control

All aspects of data analysis were conducted according to standard procedures of the Research Group of Drugs in Pregnancy and Copenhagen Phase IV unit (Phase4CPH) at Center for Clinical Research and Prevention, Copenhagen University Hospital. Validation of the programming was performed. Smaller programs (3-20 lines of coding) were reviewed by an independent statistical programmer and longer programs were recoded by an independent statistical programmer.

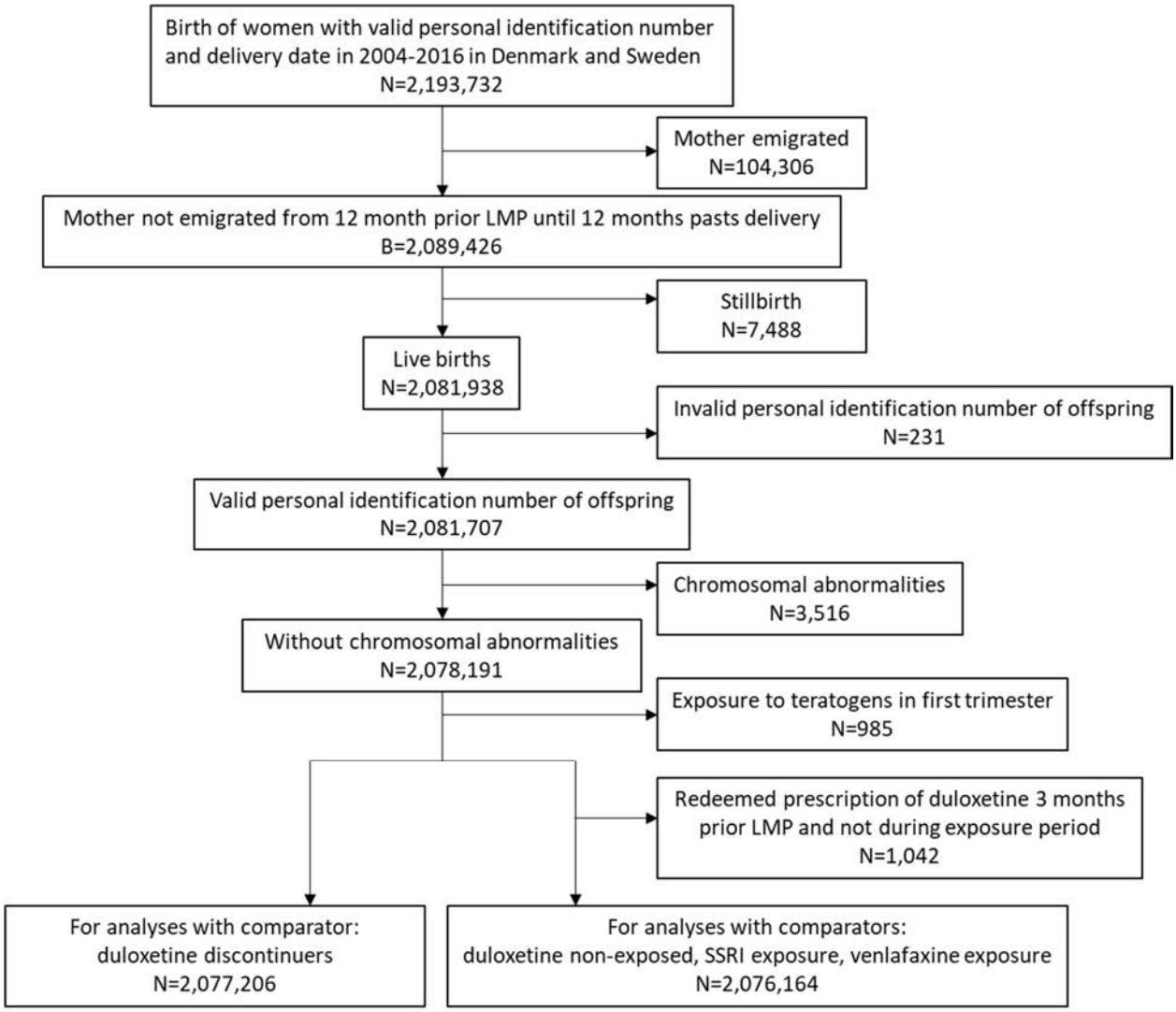
10. Results

10.1. Participants

The final cohorts used for the analyses are either based on pregnancies ending with births in Sweden and Denmark (outcomes: malformation, stillbirth, SGA and preterm birth) or pregnancies ending with abortion or birth in Denmark (outcomes: spontaneous or elective abortion). Below are the flowcharts of the construction of the final cohorts for analyses of malformation, spontaneous abortion, elective abortion, stillbirth, SGA and preterm birth.

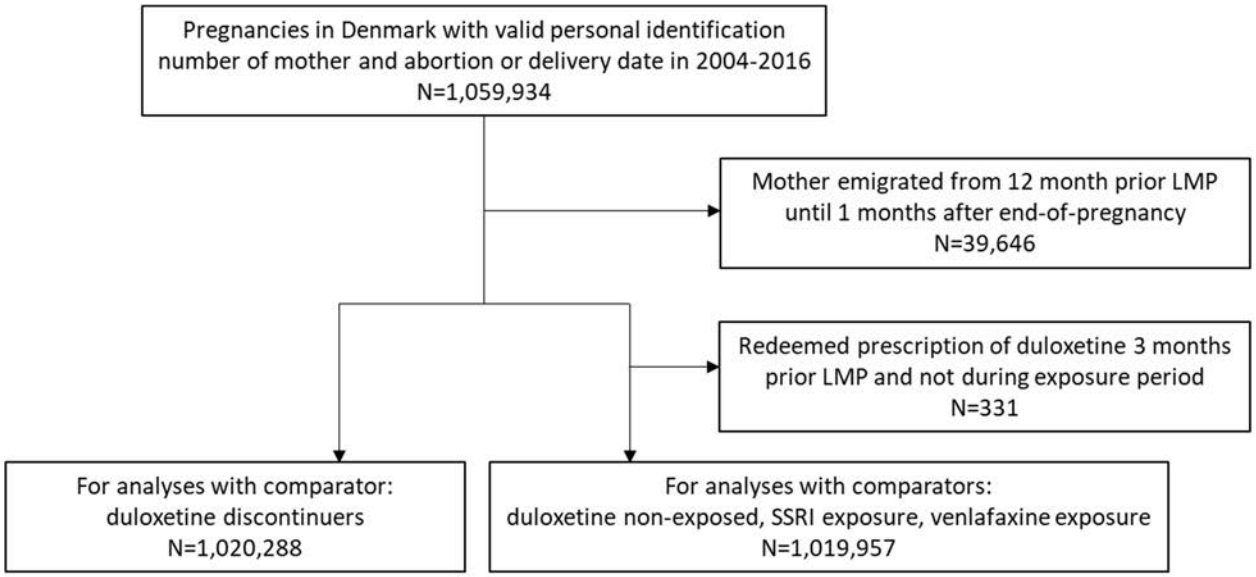
10.1.1. Flowchart for population used for malformation analyses

For the analyses using duloxetine non-exposed, SSRI exposed, and venlafaxine exposed as comparators, women with a redeemed prescription of duloxetine 3 months prior to the LMP (but not during pregnancy) were excluded from the population. This was to ensure that the comparison groups were not exposed to duloxetine during pregnancy. For the analyses using duloxetine discontinuers as comparator, women with a redeemed prescription of duloxetine 3 months prior to the LMP (but not during pregnancy) were not excluded, to identify as many women as possible with an exposure to duloxetine prior to pregnancy.


Birth of women with valid personal identification number and delivery date in 2004-2016 in Denmark and Sweden
N=2,193,732
Mother emigrated
N=104,306
Mother not emigrated from 12 month prior LMP until 12 months pasts delivery
B=2,089,426
Stillbirth
N=7,488
Live births
N=2,081,938
Invalid personal identification number of offspring
N=231
Valid personal identification number of offspring
N=2,081,707
Chromosomal abnormalities
N=3,516
Without chromosomal abnormalities
N=2,078,191
Exposure to teratogens in first trimester
N=985
Redeemed prescription of duloxetine 3 months prior LMP and not during exposure period
N=1,042
For analyses with comparator:
duloxetine discontinuers
N=2,077,206
For analyses with comparators:
duloxetine non-exposed, SSRI exposure, venlafaxine exposure
N=2,076,164

10.1.2. Flowchart for population used for abortion analyses

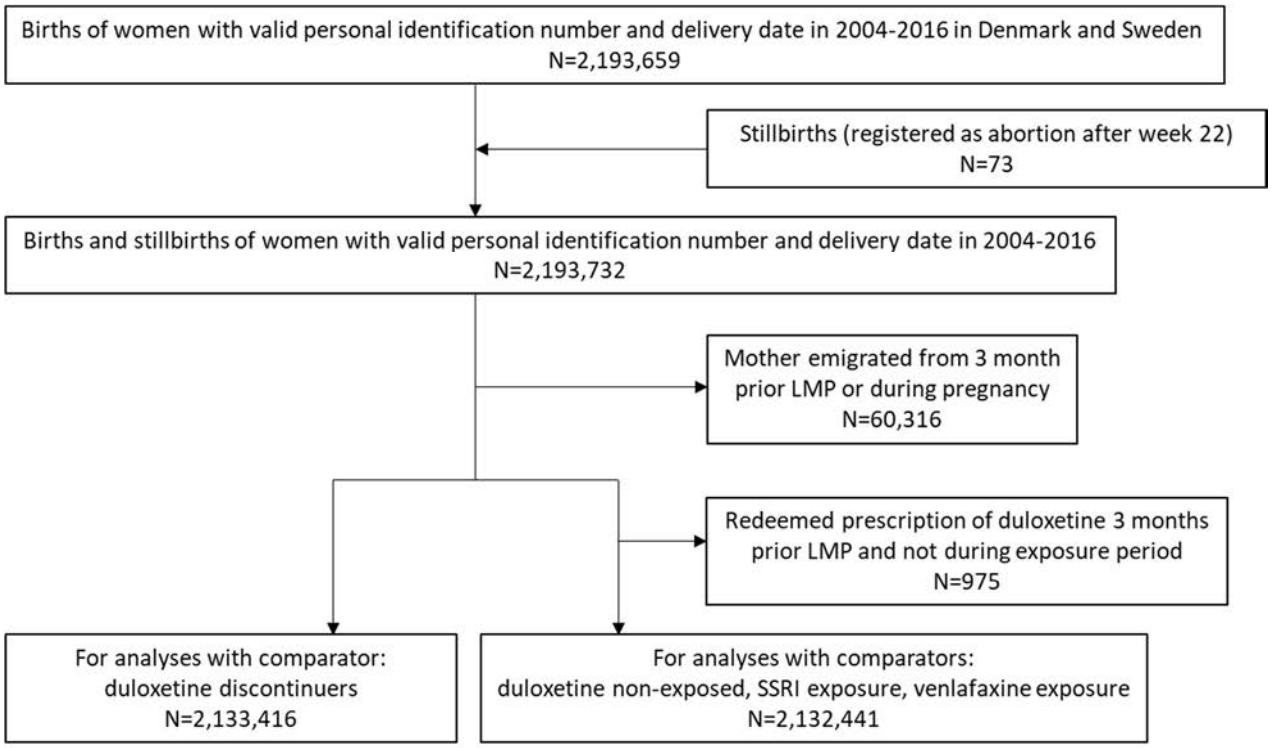
For the analyses using duloxetine non-exposed, SSRI exposed, and venlafaxine exposed as comparators, women with a redeemed prescription of duloxetine 3 months prior to the LMP (but not during pregnancy) were excluded from the population. This was to ensure that the comparison groups were not exposed to duloxetine during pregnancy. For the analyses using duloxetine discontinuers as comparator, women with a redeemed prescription of duloxetine 3 months prior to the LMP (but not during pregnancy) were not excluded, to identify as many women as possible with an exposure to duloxetine prior to pregnancy.



10.1.3. Flowchart for population used for stillbirth analyses

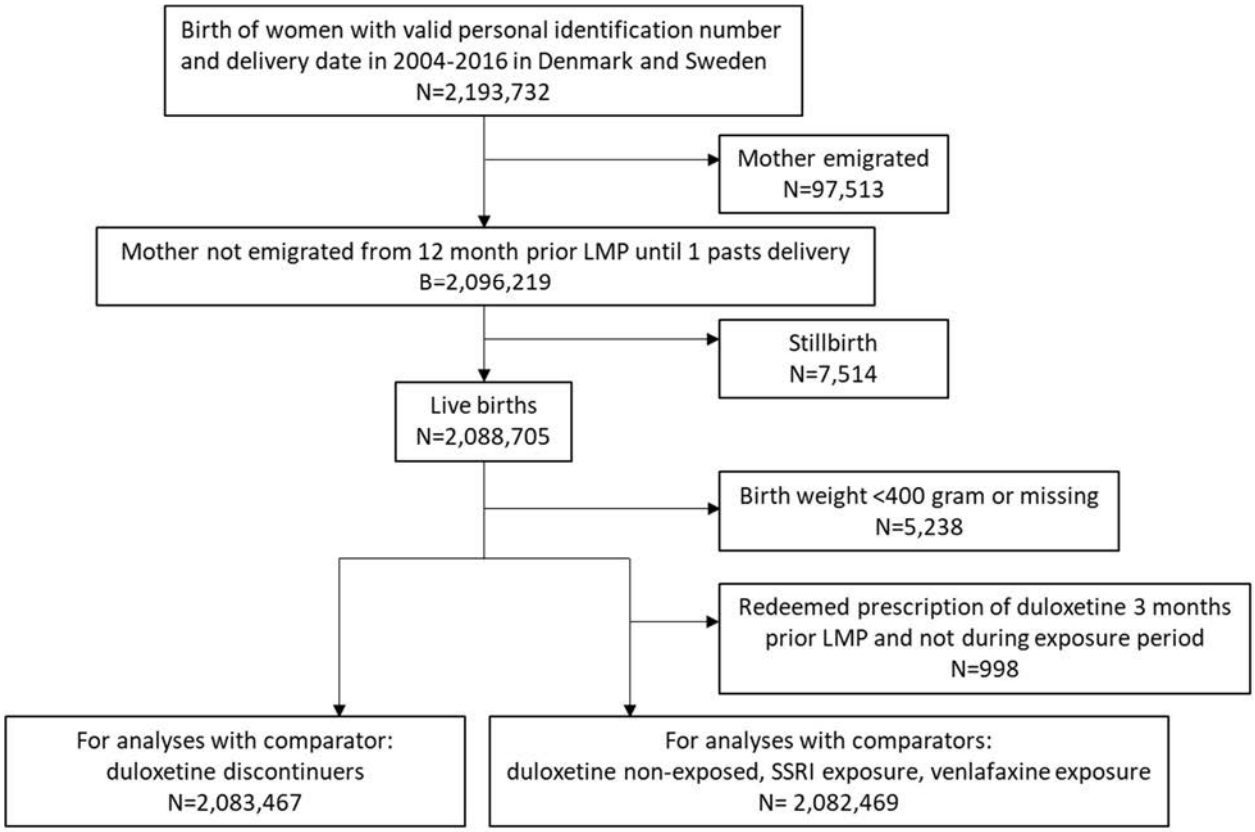
For the analyses using duloxetine non-exposed, SSRI exposed, and venlafaxine exposed as comparators, women with a redeemed prescription of duloxetine 3 months prior to the LMP (but not during pregnancy) were excluded from the population. This was to ensure that the comparison groups were not exposed to duloxetine during pregnancy. For the analyses using duloxetine discontinuers as comparator, women with a redeemed prescription of duloxetine 3 months prior to the LMP (but not during pregnancy) were not excluded, to identify as many women as possible with an exposure to duloxetine prior to pregnancy.

Abortions after week 22 were considered as stillbirths. Stillbirth cases from both medical birth registers and national patient registers were included in the analyses of stillbirth.



10.1.4. Flowchart for population used for small for gestational age and preterm birth analyses

For the analyses using duloxetine non-exposed, SSRI exposed, and venlafaxine exposed as comparators, women with a redeemed prescription of duloxetine 3 months prior to the LMP (but not during pregnancy) were excluded from the population. This was to ensure that the comparison groups were not exposed to duloxetine during pregnancy. For the analyses using duloxetine discontinuers as comparator, women with a redeemed prescription of duloxetine 3 months prior to the LMP (but not during pregnancy) were not excluded, to identify as many women as possible with an exposure to duloxetine prior to pregnancy.



10.2. Descriptive data

The population is defined differently for each outcome (see flowcharts in Section 10.1). Below are tables with characteristics of the population used in the various analyses for the primary outcome of malformation presented. As the analyses are repeated with varying comparison groups (duloxetine non-exposed, SSRI exposed, venlafaxine exposed, duloxetine discontinuers), a baseline table for each comparison group is presented. The tables also include characteristics of the population after PS matching, as well as standardized differences to assess the balance of the characteristics before and after matching.

Corresponding tables for the remaining outcomes (stillbirth, SGA and preterm birth) when the exposure is defined as >1 redeemed prescription in the relevant exposure time period is included in the Supplementary material.

The Supplementary material also holds corresponding tables with background characteristics for the populations used in the sensitivity analyses and information on missing values (table S4).

10.2.1. Background characteristics for analyses of malformation (major and minor)

10.2.1.1. Background characteristics. Analyses: Malformation. Comparison group: non-exposed to duloxetine.

Variable	Value	Non exposed	Duloxetine	Std. diff.	Non exposed PS sample	Duloxetine PS sample	Std. diff. PS sample
Age, continuous (mean)				0.15			0.04
		30.2 (26.7; 33.7)	30.8 (27.2; 35.1)		30.8 (26.8; 34.7)	30.7 (27.2; 35.0)	
Age, grouped				0.16			0.05
	18-24 years	323541 (15.6%)	231 (15.3%)		888 (15.4%)	222 (15.4%)	
	25-29 years	684195 (33.0%)	447 (29.6%)		1659 (28.8%)	429 (29.8%)	
	30-34 years	591115 (28.5%)	379 (25.1%)		1532 (26.6%)	359 (25.0%)	

Variable	Value	Non exposed	Duloxetine	Std. diff.	Non exposed PS sample	Duloxetine PS sample	Std. diff. PS sample
	35-60 years	475801 (22.9%)	455 (30.1%)		1672 (29.1%)	428 (29.8%)	
BMI, continuous (mean)				0.38			0.11
		23.5 (21.3; 26.7)	25.4 (22.3; 30.0)		24.6 (21.9; 28.9)	25.4 (22.3; 29.8)	
BMI, grouped				0.39			0.12
	BMI <21	422401 (21.7%)	210 (14.9%)		953 (17.3%)	206 (14.9%)	
	BMI 21-26<	953277 (49.1%)	555 (39.3%)		2354 (42.6%)	545 (39.5%)	
	BMI 26-30<	323197 (16.6%)	294 (20.8%)		1047 (19.0%)	287 (20.8%)	
	BMI >=30	243826 (12.6%)	353 (25.0%)		1169 (21.2%)	342 (24.8%)	
Household income				0.41			0.00
	income quartile1	458644 (22.2%)	569 (37.8%)		2189 (38.1%)	549 (38.2%)	
	income quartile2	514943 (25.0%)	391 (25.9%)		1481 (25.8%)	370 (25.7%)	
	income quartile3	547822 (26.6%)	317 (21.0%)		1222 (21.2%)	300 (20.9%)	
	income quartile4	540500 (26.2%)	230 (15.3%)		859 (14.9%)	219 (15.2%)	
Education				0.40			0.05
	< 11 years	252162 (12.3%)	341 (22.7%)		1462 (25.4%)	327 (22.7%)	
	11-15 years	1000210 (48.8%)	806 (53.7%)		3010 (52.3%)	771 (53.6%)	
	>16 years	797606 (38.9%)	355 (23.6%)		1279 (22.2%)	340 (23.6%)	
Smoking				0.34			-0.06

Variable	Value	Non exposed	Duloxetine	Std. diff.	Non exposed PS sample	Duloxetine PS sample	Std. diff. PS sample
	NO	1822136 (91.0%)	1152 (79.3%)		4412 (76.7%)	1140 (79.3%)	
	YES	179398 (9.0%)	301 (20.7%)		1339 (23.3%)	298 (20.7%)	
Data source				0.06			-0.02
	0	749984 (36.1%)	502 (33.2%)		1851 (32.2%)	479 (33.3%)	
	1	1324668 (63.9%)	1010 (66.8%)		3900 (67.8%)	959 (66.7%)	
Previous stillbirth				-0.02			-0.10
	0	2064251 (99.5%)	1506 (99.6%)		5675 (98.7%)	1432 (99.6%)	
	1	10401 (0.5%)	6 (0.4%)		76 (1.3%)	6 (0.4%)	
Parity				0.25			0.11
	0	943927 (45.7%)	711 (47.2%)		2502 (43.6%)	663 (46.3%)	
	1	747860 (36.2%)	401 (26.6%)		1845 (32.2%)	390 (27.2%)	
	2	269308 (13.0%)	254 (16.9%)		846 (14.8%)	244 (17.0%)	
	>2	105852 (5.1%)	140 (9.3%)		541 (9.4%)	135 (9.4%)	
Prev. spontaneous abortions				0.09			0.10
	0	1654343 (79.7%)	1186 (78.4%)		4273 (74.3%)	1126 (78.3%)	
	1	335312 (16.2%)	238 (15.7%)		1045 (18.2%)	228 (15.9%)	
	2+	84997 (4.1%)	88 (5.8%)		433 (7.5%)	84 (5.8%)	
Outpatient visits, continuous				0.13			-0.04
		0.0 (0.0; 0.0)	0.0 (0.0; 0.0)		0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	

Variable	Value	Non exposed	Duloxetine	Std. diff.	Non exposed PS sample	Duloxetine PS sample	Std. diff. PS sample
Outpatient visits, grouped				0.17			0.06
	0	1988265 (95.8%)	1390 (91.9%)		5246 (91.2%)	1325 (92.1%)	
	1	60078 (2.9%)	89 (5.9%)		318 (5.5%)	83 (5.8%)	
	>1	26309 (1.3%)	33 (2.2%)		187 (3.3%)	30 (2.1%)	
Hospital, continuous				0.24			-0.01
		0.0 (0.0; 0.0)	0.0 (0.0; 0.0)		0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	
Hospital, grouped				0.29			0.00
	0	1924859 (92.8%)	1286 (85.1%)		4920 (85.6%)	1230 (85.5%)	
	1	115773 (5.6%)	152 (10.1%)		564 (9.8%)	141 (9.8%)	
	>1	34020 (1.6%)	74 (4.9%)		267 (4.6%)	67 (4.7%)	
Emergency depart., continuous				0.12			0.02
		0.0 (0.0; 0.0)	0.0 (0.0; 0.0)		0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	
Emergency depart., grouped				0.20			0.06
	0	2007115 (96.7%)	1430 (94.6%)		5491 (95.5%)	1358 (94.4%)	
	1	53990 (2.6%)	51 (3.4%)		161 (2.8%)	50 (3.5%)	
	>1	13547 (0.7%)	31 (2.1%)		99 (1.7%)	30 (2.1%)	

Variable	Value	Non exposed	Duloxetine	Std. diff.	Non exposed PS sample	Duloxetine PS sample	Std. diff. PS sample
Psychiatric outpatient, continuous				0.59			0.04
		0.0 (0.0; 0.0)	0.0 (0.0; 1.0)		0.0 (0.0; 1.0)	0.0 (0.0; 1.0)	
Psychiatric outpatient, grouped				0.88			-0.01
	0	2046478 (98.6%)	1043 (69.0%)		3963 (68.9%)	998 (69.4%)	
	1+	28174 (1.4%)	469 (31.0%)		1788 (31.1%)	440 (30.6%)	
Psychiatric hospital, continuous				0.29			0.04
		0.0 (0.0; 0.0)	0.0 (0.0; 0.0)		0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	
Psychiatric hospital, grouped				0.35			0.05
	0	2070449 (99.8%)	1416 (93.7%)		5470 (95.1%)	1351 (93.9%)	
	1+	4203 (0.2%)	96 (6.3%)		281 (4.9%)	87 (6.1%)	
Gestational diabetes during index pregnancy				0.17			-0.10
	0	2024065 (97.6%)	1424 (94.2%)		5279 (91.8%)	1357 (94.4%)	
	1	50587 (2.4%)	88 (5.8%)		472 (8.2%)	81 (5.6%)	

Variable	Value	Non exposed	Duloxetine	Std. diff.	Non exposed PS sample	Duloxetine PS sample	Std. diff. PS sample
Diabetes				0.10			-0.13
	NO	2049252 (98.8%)	1472 (97.4%)		5464 (95.0%)	1402 (97.5%)	
	YES	25400 (1.2%)	40 (2.6%)		287 (5.0%)	36 (2.5%)	
Hyper or hypothyroidism				0.19			-0.09
	NO	2018545 (97.3%)	1412 (93.4%)		5234 (91.0%)	1342 (93.3%)	
	YES	56107 (2.7%)	100 (6.6%)		517 (9.0%)	96 (6.7%)	
Hypertension				0.08			-0.08
	NO	2067886 (99.7%)	1498 (99.1%)		5644 (98.1%)	1425 (99.1%)	
	YES	6766 (0.3%)	14 (0.9%)		107 (1.9%)	13 (0.9%)	
Obesity				0.19			-0.04
	NO	2010966 (96.9%)	1401 (92.7%)		5249 (91.3%)	1330 (92.5%)	
	YES	63686 (3.1%)	111 (7.3%)		502 (8.7%)	108 (7.5%)	
Depression				0.93			-0.05
	NO	2035521 (98.1%)	995 (65.8%)		3669 (63.8%)	952 (66.2%)	
	YES	39131 (1.9%)	517 (34.2%)		2082 (36.2%)	486 (33.8%)	
Affective disorder				0.25			0.05
	NO	2071485 (99.8%)	1459 (96.5%)		5600 (97.4%)	1388 (96.5%)	
	YES	3167 (0.2%)	53 (3.5%)		151 (2.6%)	50 (3.5%)	
Anxiety or phobia				0.48			-0.02
	NO	2055365 (99.1%)	1319 (87.2%)		4982 (86.6%)	1257 (87.4%)	
	YES	19287 (0.9%)	193 (12.8%)		769 (13.4%)	181 (12.6%)	

Variable	Value	Non exposed	Duloxetine	Std. diff.	Non exposed PS sample	Duloxetine PS sample	Std. diff. PS sample
Severe stress reaction				0.44			0.02
	NO	2053419 (99.0%)	1341 (88.7%)		5175 (90.0%)	1285 (89.4%)	
	YES	21233 (1.0%)	171 (11.3%)		576 (10.0%)	153 (10.6%)	
Stress urinary incontinence				0			0
	NO	2074652 (100.0%)	1512 (100.0%)		5751 (100.0%)	1438 (100.0%)	
Renal failure				0.01			-0.02
	NO	2073579 (99.9%)	1511 (99.9%)		5744 (99.9%)	1437 (99.9%)	
	YES	1073 (0.1%)	<5 (0%)		7 (0.1%)	<5 (0%)	
Triamcinolone				0.05			0.04
	NO	2074088 (100.0%)	1509 (99.8%)		5747 (99.9%)	1435 (99.8%)	
	YES	564 (0.0%)	<5 (0%)		<5 (0%)	<5 (0%)	
Dexamethasone				-0.01			0
	NO	2074616 (100.0%)	1512 (100.0%)		5751 (100.0%)	1438 (100.0%)	
	YES	36 (0.0%)	<5 (0%)				
Cortisone				0.05			-0.03
	NO	2063768 (99.5%)	1497 (99.0%)		5671 (98.6%)	1423 (99.0%)	
	YES	10884 (0.5%)	15 (1.0%)		80 (1.4%)	15 (1.0%)	
Prednisolone				0.07			-0.06
	NO	2057789 (99.2%)	1489 (98.5%)		5614 (97.6%)	1415 (98.4%)	
	YES	16863 (0.8%)	23 (1.5%)		137 (2.4%)	23 (1.6%)	

Variable	Value	Non exposed	Duloxetine	Std. diff.	Non exposed PS sample	Duloxetine PS sample	Std. diff. PS sample
Budesonide				0.07			0.07
	NO	2074176 (100.0%)	1507 (99.7%)		5748 (99.9%)	1433 (99.7%)	
	YES	476 (0.0%)	5 (0.3%)		<5 (0%)	5 (0.3%)	
Glucose lowering				0.08			-0.13
	NO	2053926 (99.0%)	1483 (98.1%)		5512 (95.8%)	1411 (98.1%)	
	YES	20726 (1.0%)	29 (1.9%)		239 (4.2%)	27 (1.9%)	
Anti hypertensive				0.24			-0.03
	NO	2056617 (99.1%)	1438 (95.1%)		5430 (94.4%)	1368 (95.1%)	
	YES	18035 (0.9%)	74 (4.9%)		321 (5.6%)	70 (4.9%)	
Fluconazole				0.11			-0.08
	NO	2036595 (98.2%)	1458 (96.4%)		5462 (95.0%)	1388 (96.5%)	
	YES	38057 (1.8%)	54 (3.6%)		289 (5.0%)	50 (3.5%)	
Mometasone				0.19			0.00
	NO	2025753 (97.6%)	1419 (93.8%)		5397 (93.8%)	1349 (93.8%)	
	YES	48899 (2.4%)	93 (6.2%)		354 (6.2%)	89 (6.2%)	
Estradiol				0.04			-0.01
	NO	1958599 (94.4%)	1413 (93.5%)		5376 (93.5%)	1347 (93.7%)	
	YES	116053 (5.6%)	99 (6.5%)		375 (6.5%)	91 (6.3%)	

Variable	Value	Non exposed	Duloxetine	Std. diff.	Non exposed PS sample	Duloxetine PS sample	Std. diff. PS sample
Medroxy progesterone				-0.02			-0.06
	NO	2058374 (99.2%)	1503 (99.4%)		5681 (98.8%)	1429 (99.4%)	
	YES	16278 (0.8%)	9 (0.6%)		70 (1.2%)	9 (0.6%)	
Hydroxy progesterone				0			0
	NO	2074652 (100.0%)	1512 (100.0%)		5751 (100.0%)	1438 (100.0%)	
Progesterone				-0.09			-0.15
	NO	1997998 (96.3%)	1479 (97.8%)		5484 (95.4%)	1409 (98.0%)	
	YES	76654 (3.7%)	33 (2.2%)		267 (4.6%)	29 (2.0%)	
Danazol				-0.00			0
	NO	2074651 (100.0%)	1512 (100.0%)		5751 (100.0%)	1438 (100.0%)	
	YES	<5 (0%)	<5 (0%)				
Betamethasone				0.07			-0.04
	NO	2064551 (99.5%)	1495 (98.9%)		5659 (98.4%)	1421 (98.8%)	
	YES	10101 (0.5%)	17 (1.1%)		92 (1.6%)	17 (1.2%)	
Prednisone				-0.03			-0.04
	NO	2073520 (99.9%)	1512 (100.0%)		5747 (99.9%)	1438 (100.0%)	
	YES	1132 (0.1%)	<5 (0%)		<5 (0%)	<5 (0%)	
Thyroid				0.19			-0.07
	NO	2016273 (97.2%)	1407 (93.1%)		5241 (91.1%)	1337 (93.0%)	
	YES	58379 (2.8%)	105 (6.9%)		510 (8.9%)	101 (7.0%)	

Variable	Value	Non exposed	Duloxetine	Std. diff.	Non exposed PS sample	Duloxetine PS sample	Std. diff. PS sample
Antithyroid				-0.02			-0.06
	NO	2072213 (99.9%)	1511 (99.9%)		5731 (99.7%)	1437 (99.9%)	
	YES	2439 (0.1%)	<5 (0%)		20 (0.3%)	<5 (0%)	
Propylthiouracil				-0.04			-0.07
	NO	2073238 (99.9%)	1512 (100.0%)		5738 (99.8%)	1438 (100.0%)	
	YES	1414 (0.1%)	<5 (0%)		13 (0.2%)	<5 (0%)	
Methimazole				0.00			-0.04
	NO	2073324 (99.9%)	1511 (99.9%)		5739 (99.8%)	1437 (99.9%)	
	YES	1328 (0.1%)	<5 (0%)		12 (0.2%)	<5 (0%)	
NSAID				0.36			-0.05
	NO	1982422 (95.6%)	1284 (84.9%)		4804 (83.5%)	1227 (85.3%)	
	YES	92230 (4.4%)	228 (15.1%)		947 (16.5%)	211 (14.7%)	
Opioids				0.51			-0.03
	NO	2031063 (97.9%)	1262 (83.5%)		4734 (82.3%)	1200 (83.4%)	
	YES	43589 (2.1%)	250 (16.5%)		1017 (17.7%)	238 (16.6%)	
Triptans				0.25			-0.03
	NO	2053197 (99.0%)	1431 (94.6%)		5395 (93.8%)	1359 (94.5%)	
	YES	21455 (1.0%)	81 (5.4%)		356 (6.2%)	79 (5.5%)	
Antiepileptics				0.55			0.12
	NO	2063142 (99.4%)	1290 (85.3%)		5148 (89.5%)	1230 (85.5%)	
	YES	11510 (0.6%)	222 (14.7%)		603 (10.5%)	208 (14.5%)	

Variable	Value	Non exposed	Duloxetine	Std. diff.	Non exposed PS sample	Duloxetine PS sample	Std. diff. PS sample
Antipsychotics				0.48			0.08
	NO	2067609 (99.7%)	1341 (88.7%)		5228 (90.9%)	1274 (88.6%)	
	YES	7043 (0.3%)	171 (11.3%)		523 (9.1%)	164 (11.4%)	
Anxiolytics				0.67			0.06
	NO	2053070 (99.0%)	1193 (78.9%)		4691 (81.6%)	1137 (79.1%)	
	YES	21582 (1.0%)	319 (21.1%)		1060 (18.4%)	301 (20.9%)	
Corticosteroid (combination)				0.21			-0.05
	NO	1985764 (95.7%)	1367 (90.4%)		5107 (88.8%)	1297 (90.2%)	
	YES	88888 (4.3%)	145 (9.6%)		644 (11.2%)	141 (9.8%)	
Fluticasone				0.03			-0.00
	NO	2069647 (99.8%)	1506 (99.6%)		5727 (99.6%)	1432 (99.6%)	
	YES	5005 (0.2%)	6 (0.4%)		24 (0.4%)	6 (0.4%)	
Progesterone (combination)				-0.09			-0.15
	NO	1986049 (95.7%)	1471 (97.3%)		5436 (94.5%)	1401 (97.4%)	
	YES	88603 (4.3%)	41 (2.7%)		315 (5.5%)	37 (2.6%)	
Antithyroid (combination)				-0.02			-0.06
	NO	2072213 (99.9%)	1511 (99.9%)		5731 (99.7%)	1437 (99.9%)	
	YES	2439 (0.1%)	<5 (0%)		20 (0.3%)	<5 (0%)	

Variable	Value	Non exposed	Duloxetine	Std. diff.	Non exposed PS sample	Duloxetine PS sample	Std. diff. PS sample
SSRI				-0.20			-0.62
	NO	2034693 (98.1%)	1512 (100.0%)		4828 (84.0%)	1438 (100.0%)	
	YES	39959 (1.9%)	<5 (0%)		923 (16.0%)	<5 (0%)	
venlafaxine				-0.07			-0.25
	NO	2069412 (99.7%)	1512 (100.0%)		5578 (97.0%)	1438 (100.0%)	
	YES	5240 (0.3%)	<5 (0%)		173 (3.0%)	<5 (0%)	

Numbers show number of pregnancies (percentage) or median (interquartile range).

Propensity score base on: data source (Sweden/Denmark), age (grouped), education grouped, household income, year (grouped), psychiatric hospital, psychiatric outpatient, smoking, previous spontaneous abortion, previous stillbirth, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, renal failure, depression, affective disorder, anxiety or phobia, severe stress reaction, diabetic peripheral neuropathic pain, glucose lowering, antihypertensive, fluconazole, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination)

10.2.1.2. Background characteristics. Analyses: Malformation. Comparison group: SSRI exposed.

Variable	Value	SSRI	Duloxetine	Std. diff.	SSRI PS sample	Duloxetine PS sample	Std. diff. PS sample
Age, continuous (mean)				0.08			0.08
		30.6 (26.8; 34.4)	30.8 (27.2; 35.1)		30.4 (26.6; 34.5)	30.7 (27.2; 35.0)	
Age, grouped				0.06			0.04
	18-24 years	6399 (16.0%)	231 (15.3%)		469 (16.3%)	222 (15.4%)	
	25-29 years	11740 (29.4%)	447 (29.6%)		887 (30.9%)	428 (29.8%)	

Variable	Value	SSRI	Duloxetine	Std. diff.	SSRI PS sample	Duloxetine PS sample	Std. diff. PS sample
	30-34 years	10855 (27.2%)	379 (25.1%)		704 (24.5%)	359 (25.0%)	
	35-60 years	10965 (27.4%)	455 (30.1%)		814 (28.3%)	428 (29.8%)	
BMI, continuous (mean)				0.18			0.10
		24.3 (21.8; 28.3)	25.4 (22.3; 30.0)		24.8 (22.0; 29.1)	25.4 (22.3; 29.9)	
BMI, grouped				0.17			0.09
	BMI <21	6878 (18.3%)	210 (14.9%)		471 (16.9%)	206 (14.9%)	
	BMI 21-26<	16598 (44.2%)	555 (39.3%)		1182 (42.3%)	545 (39.5%)	
	BMI 26-30<	7120 (18.9%)	294 (20.8%)		537 (19.2%)	286 (20.7%)	
	BMI >=30	6977 (18.6%)	353 (25.0%)		604 (21.6%)	342 (24.8%)	
Household income				0.19			0.03
	income quartile1	12032 (30.3%)	569 (37.8%)		1115 (38.8%)	548 (38.1%)	
	income quartile2	10306 (26.0%)	391 (25.9%)		757 (26.3%)	370 (25.7%)	
	income quartile3	9760 (24.6%)	317 (21.0%)		610 (21.2%)	300 (20.9%)	
	income quartile4	7557 (19.1%)	230 (15.3%)		392 (13.6%)	219 (15.2%)	
Education				0.19			0.03
	< 11 years	7390 (18.6%)	341 (22.7%)		685 (23.8%)	327 (22.8%)	
	11-15 years	19650 (49.5%)	806 (53.7%)		1540 (53.6%)	770 (53.6%)	

Variable	Value	SSRI	Duloxetine	Std. diff.	SSRI PS sample	Duloxetine PS sample	Std. diff. PS sample
	>16 years	12630 (31.8%)	355 (23.6%)		649 (22.6%)	340 (23.7%)	
Smoking				0.09			0.02
	NO	31938 (82.8%)	1152 (79.3%)		2304 (80.2%)	1140 (79.3%)	
	YES	6640 (17.2%)	301 (20.7%)		570 (19.8%)	297 (20.7%)	
Data source				0.04			0.03
	0	13984 (35.0%)	502 (33.2%)		993 (34.6%)	479 (33.3%)	
	1	25975 (65.0%)	1010 (66.8%)		1881 (65.4%)	958 (66.7%)	
Previous stillbirth				-0.03			0.02
	0	39709 (99.4%)	1506 (99.6%)		2866 (99.7%)	1431 (99.6%)	
	1	250 (0.6%)	6 (0.4%)		8 (0.3%)	6 (0.4%)	
Parity				0.17			0.16
	0	18711 (47.0%)	711 (47.2%)		1337 (46.7%)	663 (46.3%)	
	1	12997 (32.6%)	401 (26.6%)		915 (31.9%)	389 (27.2%)	
	2	5486 (13.8%)	254 (16.9%)		401 (14.0%)	244 (17.1%)	
	>2	2618 (6.6%)	140 (9.3%)		213 (7.4%)	135 (9.4%)	
Prev. spontaneous abortions				0.05			0.05
	0	31098 (77.8%)	1186 (78.4%)		2299 (80.0%)	1125 (78.3%)	
	1	6867 (17.2%)	238 (15.7%)		432 (15.0%)	228 (15.9%)	

Variable	Value	SSRI	Duloxetine	Std. diff.	SSRI PS sample	Duloxetine PS sample	Std. diff. PS sample
	2+	1994 (5.0%)	88 (5.8%)		143 (5.0%)	84 (5.8%)	
Outpatient visits, continuous				0.04			-0.02
		0.0 (0.0; 0.0)	0.0 (0.0; 0.0)		0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	
Outpatient visits, grouped				0.11			0.00
	0	37333 (93.4%)	1390 (91.9%)		2632 (91.6%)	1324 (92.1%)	
	1	1777 (4.4%)	89 (5.9%)		163 (5.7%)	83 (5.8%)	
	>1	849 (2.1%)	33 (2.2%)		79 (2.7%)	30 (2.1%)	
Hospital, continuous				0.12			-0.02
		0.0 (0.0; 0.0)	0.0 (0.0; 0.0)		0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	
Hospital, grouped				0.12			0.05
	0	35722 (89.4%)	1286 (85.1%)		2447 (85.1%)	1230 (85.6%)	
	1	2985 (7.5%)	152 (10.1%)		283 (9.8%)	141 (9.8%)	
	>1	1252 (3.1%)	74 (4.9%)		144 (5.0%)	66 (4.6%)	
Emergency depart., continuous				-0.00			-0.04
		0.0 (0.0; 0.0)	0.0 (0.0; 0.0)		0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	
Emergency depart., grouped				0.05			0.08
	0	37719 (94.4%)	1430 (94.6%)		2692 (93.7%)	1357 (94.4%)	

Variable	Value	SSRI	Duloxetine	Std. diff.	SSRI PS sample	Duloxetine PS sample	Std. diff. PS sample
	1	1554 (3.9%)	51 (3.4%)		115 (4.0%)	50 (3.5%)	
	>1	686 (1.7%)	31 (2.1%)		67 (2.3%)	30 (2.1%)	
Psychiatric outpatient, continuous				0.29			0.06
		0.0 (0.0; 0.0)	0.0 (0.0; 1.0)		0.0 (0.0; 1.0)	0.0 (0.0; 1.0)	
Psychiatric outpatient, grouped				0.34			0.02
	0	33236 (83.2%)	1043 (69.0%)		2016 (70.1%)	998 (69.5%)	
	1+	6723 (16.8%)	469 (31.0%)		858 (29.9%)	439 (30.5%)	
Psychiatric hospital, continuous				0.17			0.03
		0.0 (0.0; 0.0)	0.0 (0.0; 0.0)		0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	
Psychiatric hospital, grouped				0.20			0.02
	0	39020 (97.7%)	1416 (93.7%)		2716 (94.5%)	1351 (94.0%)	
	1+	939 (2.3%)	96 (6.3%)		158 (5.5%)	86 (6.0%)	
Gestational diabetes during index pregnancy				0.10			-0.01
	0	38463 (96.3%)	1424 (94.2%)		2706 (94.2%)	1356 (94.4%)	
	1	1496 (3.7%)	88 (5.8%)		168 (5.8%)	81 (5.6%)	

Variable	Value	SSRI	Duloxetine	Std. diff.	SSRI PS sample	Duloxetine PS sample	Std. diff. PS sample
Diabetes				0.05			0.03
	NO	39176 (98.0%)	1472 (97.4%)		2815 (97.9%)	1401 (97.5%)	
	YES	783 (2.0%)	40 (2.6%)		59 (2.1%)	36 (2.5%)	
Hyper or hypothyroidism				0.07			0.03
	NO	37948 (95.0%)	1412 (93.4%)		2701 (94.0%)	1341 (93.3%)	
	YES	2011 (5.0%)	100 (6.6%)		173 (6.0%)	96 (6.7%)	
Hypertension				0.04			0.00
	NO	39719 (99.4%)	1498 (99.1%)		2848 (99.1%)	1424 (99.1%)	
	YES	240 (0.6%)	14 (0.9%)		26 (0.9%)	13 (0.9%)	
Obesity				0.09			0.00
	NO	37900 (94.8%)	1401 (92.7%)		2660 (92.6%)	1329 (92.5%)	
	YES	2059 (5.2%)	111 (7.3%)		214 (7.4%)	108 (7.5%)	
Depression				0.37			-0.02
	NO	32633 (81.7%)	995 (65.8%)		1872 (65.1%)	952 (66.2%)	
	YES	7326 (18.3%)	517 (34.2%)		1002 (34.9%)	485 (33.8%)	
Affective disorder				0.14			0.03
	NO	39406 (98.6%)	1459 (96.5%)		2788 (97.0%)	1387 (96.5%)	
	YES	553 (1.4%)	53 (3.5%)		86 (3.0%)	50 (3.5%)	

Variable	Value	SSRI	Duloxetine	Std. diff.	SSRI PS sample	Duloxetine PS sample	Std. diff. PS sample
Anxiety or phobia				0.08			0.02
	NO	35937 (89.9%)	1319 (87.2%)		2533 (88.1%)	1256 (87.4%)	
	YES	4022 (10.1%)	193 (12.8%)		341 (11.9%)	181 (12.6%)	
Severe stress reaction				0.23			0.01
	NO	37949 (95.0%)	1341 (88.7%)		2578 (89.7%)	1284 (89.4%)	
	YES	2010 (5.0%)	171 (11.3%)		296 (10.3%)	153 (10.6%)	
Stress urinary incontinence				0			0
	NO	39959 (100.0%)	1512 (100.0%)		2874 (100.0%)	1437 (100.0%)	
Renal failure				-0.01			0.02
	NO	39920 (99.9%)	1511 (99.9%)		2873 (100.0%)	1436 (99.9%)	
	YES	39 (0.1%)	<5 (0%)		<5 (0%)	<5 (0%)	
Triamcinolone				0.04			0.05
	NO	39934 (99.9%)	1509 (99.8%)		2873 (100.0%)	1434 (99.8%)	
	YES	25 (0.1%)	<5 (0%)		<5 (0%)	<5 (0%)	
Dexamethasone				-0.01			0
	NO	39957 (100.0%)	1512 (100.0%)		2874 (100.0%)	1437 (100.0%)	
	YES	<5 (0%)	<5 (0%)				
Cortisone				0.03			0.04
	NO	39683 (99.3%)	1497 (99.0%)		2855 (99.3%)	1422 (99.0%)	

Variable	Value	SSRI	Duloxetine	Std. diff.	SSRI PS sample	Duloxetine PS sample	Std. diff. PS sample
	YES	276 (0.7%)	15 (1.0%)		19 (0.7%)	15 (1.0%)	
Prednisolone				0.00			-0.04
	NO	39365 (98.5%)	1489 (98.5%)		2811 (97.8%)	1414 (98.4%)	
	YES	594 (1.5%)	23 (1.5%)		63 (2.2%)	23 (1.6%)	
Budesonide				0.06			0.03
	NO	39932 (99.9%)	1507 (99.7%)		2869 (99.8%)	1432 (99.7%)	
	YES	27 (0.1%)	5 (0.3%)		5 (0.2%)	5 (0.3%)	
Glucose lowering				0.02			0.02
	NO	39314 (98.4%)	1483 (98.1%)		2827 (98.4%)	1410 (98.1%)	
	YES	645 (1.6%)	29 (1.9%)		47 (1.6%)	27 (1.9%)	
Antihypertensive				0.11			0.02
	NO	38842 (97.2%)	1438 (95.1%)		2749 (95.7%)	1368 (95.2%)	
	YES	1117 (2.8%)	74 (4.9%)		125 (4.3%)	69 (4.8%)	
Fluconazole				0.04			0.02
	NO	38787 (97.1%)	1458 (96.4%)		2783 (96.8%)	1387 (96.5%)	
	YES	1172 (2.9%)	54 (3.6%)		91 (3.2%)	50 (3.5%)	
Mometasone				0.08			0.05
	NO	38193 (95.6%)	1419 (93.8%)		2729 (95.0%)	1348 (93.8%)	
	YES	1766 (4.4%)	93 (6.2%)		145 (5.0%)	89 (6.2%)	
Estradiol				-0.01			-0.03

Variable	Value	SSRI	Duloxetine	Std. diff.	SSRI PS sample	Duloxetine PS sample	Std. diff. PS sample
	NO	37259 (93.2%)	1413 (93.5%)		2674 (93.0%)	1346 (93.7%)	
	YES	2700 (6.8%)	99 (6.5%)		200 (7.0%)	91 (6.3%)	
Medroxyprogesterone				-0.02			-0.02
	NO	39642 (99.2%)	1503 (99.4%)		2852 (99.2%)	1428 (99.4%)	
	YES	317 (0.8%)	9 (0.6%)		22 (0.8%)	9 (0.6%)	
Hydroxyprogesterone				0			0
	NO	39959 (100.0%)	1512 (100.0%)		2874 (100.0%)	1437 (100.0%)	
Progesterone				-0.10			-0.10
	NO	38390 (96.1%)	1479 (97.8%)		2767 (96.3%)	1408 (98.0%)	
	YES	1569 (3.9%)	33 (2.2%)		107 (3.7%)	29 (2.0%)	
Danazol				0			0
	NO	39959 (100.0%)	1512 (100.0%)		2874 (100.0%)	1437 (100.0%)	
	YES	<5 (0%)	<5 (0%)				
Betamethasone				0.01			-0.02
	NO	39561 (99.0%)	1495 (98.9%)		2834 (98.6%)	1420 (98.8%)	
	YES	398 (1.0%)	17 (1.1%)		40 (1.4%)	17 (1.2%)	
Prednisone				-0.03			-0.05
	NO	39939 (99.9%)	1512 (100.0%)		2871 (99.9%)	1437 (100.0%)	
	YES	20 (0.1%)	<5 (0%)		<5 (0%)	<5 (0%)	

Variable	Value	SSRI	Duloxetine	Std. diff.	SSRI PS sample	Duloxetine PS sample	Std. diff. PS sample
Thyroid				0.06			0.03
	NO	37803 (94.6%)	1407 (93.1%)		2692 (93.7%)	1336 (93.0%)	
	YES	2156 (5.4%)	105 (6.9%)		182 (6.3%)	101 (7.0%)	
Antithyroid				-0.02			-0.01
	NO	39903 (99.9%)	1511 (99.9%)		2871 (99.9%)	1436 (99.9%)	
	YES	56 (0.1%)	<5 (0%)		<5 (0%)	<5 (0%)	
Propylthiouracil				-0.03			-0.05
	NO	39935 (99.9%)	1512 (100.0%)		2871 (99.9%)	1437 (100.0%)	
	YES	24 (0.1%)	<5 (0%)		<5 (0%)	<5 (0%)	
Methimazole				-0.01			0.02
	NO	39921 (99.9%)	1511 (99.9%)		2873 (100.0%)	1436 (99.9%)	
	YES	38 (0.1%)	<5 (0%)		<5 (0%)	<5 (0%)	
NSAID				0.20			0.04
	NO	36549 (91.5%)	1284 (84.9%)		2496 (86.8%)	1227 (85.4%)	
	YES	3410 (8.5%)	228 (15.1%)		378 (13.2%)	210 (14.6%)	
Opioids				0.33			-0.02
	NO	37456 (93.7%)	1262 (83.5%)		2381 (82.8%)	1200 (83.5%)	
	YES	2503 (6.3%)	250 (16.5%)		493 (17.2%)	237 (16.5%)	
Triptans				0.13			0.02
	NO	38823 (97.2%)	1431 (94.6%)		2730 (95.0%)	1358 (94.5%)	

Variable	Value	SSRI	Duloxetine	Std. diff.	SSRI PS sample	Duloxetine PS sample	Std. diff. PS sample
	YES	1136 (2.8%)	81 (5.4%)		144 (5.0%)	79 (5.5%)	
Antiepileptics				0.37			0.01
	NO	38372 (96.0%)	1290 (85.3%)		2467 (85.8%)	1230 (85.6%)	
	YES	1587 (4.0%)	222 (14.7%)		407 (14.2%)	207 (14.4%)	
Antipsychotics				0.27			0.03
	NO	38279 (95.8%)	1341 (88.7%)		2573 (89.5%)	1274 (88.7%)	
	YES	1680 (4.2%)	171 (11.3%)		301 (10.5%)	163 (11.3%)	
Anxiolytics				0.20			0.03
	NO	34541 (86.4%)	1193 (78.9%)		2309 (80.3%)	1137 (79.1%)	
	YES	5418 (13.6%)	319 (21.1%)		565 (19.7%)	300 (20.9%)	
Corticosteroid (combination)				0.07			0.03
	NO	36953 (92.5%)	1367 (90.4%)		2616 (91.0%)	1296 (90.2%)	
	YES	3006 (7.5%)	145 (9.6%)		258 (9.0%)	141 (9.8%)	
Fluticasone				0.01			-0.02
	NO	39814 (99.6%)	1506 (99.6%)		2859 (99.5%)	1431 (99.6%)	
	YES	145 (0.4%)	6 (0.4%)		15 (0.5%)	6 (0.4%)	
Progesterone (combination)				-0.10			-0.09
	NO	38156 (95.5%)	1471 (97.3%)		2753 (95.8%)	1400 (97.4%)	

Variable	Value	SSRI	Duloxetine	Std. diff.	SSRI PS sample	Duloxetine PS sample	Std. diff. PS sample
	YES	1803 (4.5%)	41 (2.7%)		121 (4.2%)	37 (2.6%)	
Antithyroid (combination)				-0.02			-0.01
	NO	39903 (99.9%)	1511 (99.9%)		2871 (99.9%)	1436 (99.9%)	
	YES	56 (0.1%)	<5 (0%)		<5 (0%)	<5 (0%)	
SSRI				.			.
	NO	<5 (0%)	1512 (100.0%)		<5 (0%)	1437 (100.0%)	
	YES	39959 (100.0%)	<5 (0%)		2874 (100.0%)	<5 (0%)	
venlafaxine				-0.19			-0.23
	NO	39249 (98.2%)	1512 (100.0%)		2803 (97.5%)	1437 (100.0%)	
	YES	710 (1.8%)	<5 (0%)		71 (2.5%)	<5 (0%)	

Numbers show number of pregnancies (percentage) or median (interquartile range).

Propensity score base on: data source (Sweden/Denmark), age (grouped), education grouped, household income, year (grouped), psychiatric hospital, psychiatric outpatient, smoking, previous spontaneous abortion, previous stillbirth, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, renal failure, depression, affective disorder, anxiety or phobia, severe stress reaction, diabetic peripheral neuropathic pain, glucose lowering, antihypertensive, fluconazole, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination)

10.2.1.3. Background characteristics. Analyses: Malformation. Comparison group: venlafaxine exposed.

Variable	Value	Venlafaxine	Duloxetine	Std. diff.	Venlafaxine PS sample	Duloxetine PS sample	Std. diff. PS sample
Age, continuous (mean)				0.09			0.07
		30.5 (26.4; 34.5)	30.8 (27.2; 35.1)		30.4 (26.3; 34.6)	30.7 (27.2; 35.0)	
Age, grouped				0.09			0.03
	18-24 years	947 (18.1%)	231 (15.3%)		240 (16.8%)	222 (15.5%)	
	25-29 years	1488 (28.4%)	447 (29.6%)		429 (30.0%)	424 (29.7%)	
	30-34 years	1359 (25.9%)	379 (25.1%)		364 (25.5%)	356 (24.9%)	
	35-60 years	1446 (27.6%)	455 (30.1%)		396 (27.7%)	427 (29.9%)	
BMI, continuous (mean)				0.05			0.04
		25.1 (22.1; 29.4)	25.4 (22.3; 30.0)		25.2 (22.3; 29.4)	25.4 (22.3; 29.8)	
BMI, grouped				0.04			0.03
	BMI <21	792 (16.1%)	210 (14.9%)		207 (15.1%)	206 (15.0%)	
	BMI 21-26<	1994 (40.5%)	555 (39.3%)		560 (40.8%)	543 (39.6%)	
	BMI 26-30<	1010 (20.5%)	294 (20.8%)		292 (21.3%)	283 (20.6%)	
	BMI >=30	1133 (23.0%)	353 (25.0%)		312 (22.8%)	340 (24.8%)	
Household income				0.05			0.05
	income quartile1	1895 (36.4%)	569 (37.8%)		569 (39.8%)	545 (38.1%)	

Variable	Value	Venlafaxine	Duloxetine	Std. diff.	Venlafaxine PS sample	Duloxetine PS sample	Std. diff. PS sample
	income quartile2	1418 (27.3%)	391 (25.9%)		369 (25.8%)	367 (25.7%)	
	income quartile3	1106 (21.3%)	317 (21.0%)		280 (19.6%)	298 (20.9%)	
	income quartile4	784 (15.1%)	230 (15.3%)		211 (14.8%)	219 (15.3%)	
Education				0.06			0.03
	< 11 years	1221 (23.5%)	341 (22.7%)		309 (21.6%)	324 (22.7%)	
	11-15 years	2641 (50.9%)	806 (53.7%)		774 (54.2%)	765 (53.5%)	
	>16 years	1326 (25.6%)	355 (23.6%)		346 (24.2%)	340 (23.8%)	
Smoking				-0.12			0.04
	NO	3779 (74.4%)	1152 (79.3%)		1157 (81.0%)	1133 (79.3%)	
	YES	1303 (25.6%)	301 (20.7%)		272 (19.0%)	296 (20.7%)	
Data source				0.22			-0.01
	0	2292 (43.7%)	502 (33.2%)		469 (32.8%)	479 (33.5%)	
	1	2948 (56.3%)	1010 (66.8%)		960 (67.2%)	950 (66.5%)	
Previous stillbirth				-0.00			0.00
	0	5218 (99.6%)	1506 (99.6%)		1423 (99.6%)	1423 (99.6%)	
	1	22 (0.4%)	6 (0.4%)		6 (0.4%)	6 (0.4%)	
Parity				0.10			0.06
	0	2546 (48.7%)	711 (47.2%)		689 (48.3%)	660 (46.4%)	
	1	1541 (29.5%)	401 (26.6%)		391 (27.4%)	387 (27.2%)	
	2	749 (14.3%)	254 (16.9%)		217 (15.2%)	242 (17.0%)	
	>2	392 (7.5%)	140 (9.3%)		130 (9.1%)	134 (9.4%)	

Variable	Value	Venlafaxine	Duloxetine	Std. diff.	Venlafaxine PS sample	Duloxetine PS sample	Std. diff. PS sample
Prev. spontaneous abortions				0.09			0.07
	0	4206 (80.3%)	1186 (78.4%)		1151 (80.5%)	1117 (78.2%)	
	1	815 (15.6%)	238 (15.7%)		196 (13.7%)	228 (16.0%)	
	2+	219 (4.2%)	88 (5.8%)		82 (5.7%)	84 (5.9%)	
Outpatient visits, continuous				0.05			0.07
		0.0 (0.0; 0.0)	0.0 (0.0; 0.0)		0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	
Outpatient visits, grouped				0.04			0.09
	0	4877 (93.1%)	1390 (91.9%)		1341 (93.8%)	1316 (92.1%)	
	1	267 (5.1%)	89 (5.9%)		63 (4.4%)	83 (5.8%)	
	>1	96 (1.8%)	33 (2.2%)		25 (1.7%)	30 (2.1%)	
Hospital, continuous				0.01			0.01
		0.0 (0.0; 0.0)	0.0 (0.0; 0.0)		0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	
Hospital, grouped				0.05			0.06
	0	4487 (85.6%)	1286 (85.1%)		1232 (86.2%)	1223 (85.6%)	
	1	509 (9.7%)	152 (10.1%)		126 (8.8%)	140 (9.8%)	
	>1	244 (4.7%)	74 (4.9%)		71 (5.0%)	66 (4.6%)	
Emergency depart., continuous				-0.07			-0.02
		0.0 (0.0; 0.0)	0.0 (0.0; 0.0)		0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	

Variable	Value	Venlafaxine	Duloxetine	Std. diff.	Venlafaxine PS sample	Duloxetine PS sample	Std. diff. PS sample
Emergency depart., grouped				0.10			0.08
	0	4854 (92.6%)	1430 (94.6%)		1337 (93.6%)	1349 (94.4%)	
	1	262 (5.0%)	51 (3.4%)		63 (4.4%)	50 (3.5%)	
	>1	124 (2.4%)	31 (2.1%)		29 (2.0%)	30 (2.1%)	
Psychiatric outpatient, continuous				0.12			-0.04
		0.0 (0.0; 0.0)	0.0 (0.0; 1.0)		0.0 (0.0; 1.0)	0.0 (0.0; 1.0)	
Psychiatric outpatient, grouped				0.16			-0.04
	0	3993 (76.2%)	1043 (69.0%)		969 (67.8%)	996 (69.7%)	
	1+	1247 (23.8%)	469 (31.0%)		460 (32.2%)	433 (30.3%)	
Psychiatric hospital, continuous				0.06			0.03
		0.0 (0.0; 0.0)	0.0 (0.0; 0.0)		0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	
Psychiatric hospital, grouped				0.06			0.03
	0	4981 (95.1%)	1416 (93.7%)		1353 (94.7%)	1344 (94.1%)	
	1+	259 (4.9%)	96 (6.3%)		76 (5.3%)	85 (5.9%)	
Gestational diabetes during index pregnancy				0.03			0.01
	0	4968 (94.8%)	1424 (94.2%)		1353 (94.7%)	1349 (94.4%)	
	1	272 (5.2%)	88 (5.8%)		76 (5.3%)	80 (5.6%)	

Variable	Value	Venlafaxine	Duloxetine	Std. diff.	Venlafaxine PS sample	Duloxetine PS sample	Std. diff. PS sample
Diabetes				0.02			0.05
	NO	5119 (97.7%)	1472 (97.4%)		1403 (98.2%)	1393 (97.5%)	
	YES	121 (2.3%)	40 (2.6%)		26 (1.8%)	36 (2.5%)	
Hyper or hypothyroidism				0.07			-0.02
	NO	4978 (95.0%)	1412 (93.4%)		1325 (92.7%)	1334 (93.4%)	
	YES	262 (5.0%)	100 (6.6%)		104 (7.3%)	95 (6.6%)	
Hypertension				0.02			0.04
	NO	5199 (99.2%)	1498 (99.1%)		1421 (99.4%)	1416 (99.1%)	
	YES	41 (0.8%)	14 (0.9%)		8 (0.6%)	13 (0.9%)	
Obesity				0.02			0.04
	NO	4877 (93.1%)	1401 (92.7%)		1336 (93.5%)	1322 (92.5%)	
	YES	363 (6.9%)	111 (7.3%)		93 (6.5%)	107 (7.5%)	
Depression				0.20			-0.05
	NO	3916 (74.7%)	995 (65.8%)		920 (64.4%)	951 (66.6%)	
	YES	1324 (25.3%)	517 (34.2%)		509 (35.6%)	478 (33.4%)	
Affective disorder				0.07			-0.02
	NO	5120 (97.7%)	1459 (96.5%)		1375 (96.2%)	1380 (96.6%)	
	YES	120 (2.3%)	53 (3.5%)		54 (3.8%)	49 (3.4%)	
Anxiety or phobia				0.10			-0.05
	NO	4732 (90.3%)	1319 (87.2%)		1227 (85.9%)	1252 (87.6%)	
	YES	508 (9.7%)	193 (12.8%)		202 (14.1%)	177 (12.4%)	

Variable	Value	Venlafaxine	Duloxetine	Std. diff.	Venlafaxine PS sample	Duloxetine PS sample	Std. diff. PS sample
Severe stress reaction				0.16			-0.02
	NO	4887 (93.3%)	1341 (88.7%)		1271 (88.9%)	1280 (89.6%)	
	YES	353 (6.7%)	171 (11.3%)		158 (11.1%)	149 (10.4%)	
Stress urinary incontinence				0			0
	NO	5240 (100.0%)	1512 (100.0%)		1429 (100.0%)	1429 (100.0%)	
Renal failure				-0.01			-0.02
	NO	5235 (99.9%)	1511 (99.9%)		1427 (99.9%)	1428 (99.9%)	
	YES	5 (0.1%)	<5 (0%)		<5 (0%)	<5 (0%)	
Triamcinolone				0.04			0.02
	NO	5237 (99.9%)	1509 (99.8%)		1427 (99.9%)	1426 (99.8%)	
	YES	<5 (0%)	<5 (0%)		<5 (0%)	<5 (0%)	
Dexamethasone				0			0
	NO	5240 (100.0%)	1512 (100.0%)		1429 (100.0%)	1429 (100.0%)	
	YES	<5 (0%)	<5 (0%)				
Cortisone				0.02			-0.01
	NO	5199 (99.2%)	1497 (99.0%)		1412 (98.8%)	1414 (99.0%)	
	YES	41 (0.8%)	15 (1.0%)		17 (1.2%)	15 (1.0%)	
Prednisolone				0.03			-0.02
	NO	5176 (98.8%)	1489 (98.5%)		1403 (98.2%)	1406 (98.4%)	
	YES	64 (1.2%)	23 (1.5%)		26 (1.8%)	23 (1.6%)	

Variable	Value	Venlafaxine	Duloxetine	Std. diff.	Venlafaxine PS sample	Duloxetine PS sample	Std. diff. PS sample
Budesonide				0.06			0.08
	NO	5236 (99.9%)	1507 (99.7%)		1429 (100.0%)	1424 (99.7%)	
	YES	<5 (0%)	5 (0.3%)		<5 (0%)	5 (0.3%)	
Glucose lowering				0.00			0.04
	NO	5141 (98.1%)	1483 (98.1%)		1409 (98.6%)	1402 (98.1%)	
	YES	99 (1.9%)	29 (1.9%)		20 (1.4%)	27 (1.9%)	
Antihypertensive				0.07			-0.01
	NO	5061 (96.6%)	1438 (95.1%)		1360 (95.2%)	1362 (95.3%)	
	YES	179 (3.4%)	74 (4.9%)		69 (4.8%)	67 (4.7%)	
Fluconazole				0.01			-0.00
	NO	5059 (96.5%)	1458 (96.4%)		1378 (96.4%)	1379 (96.5%)	
	YES	181 (3.5%)	54 (3.6%)		51 (3.6%)	50 (3.5%)	
Mometasone				0.09			0.02
	NO	5023 (95.9%)	1419 (93.8%)		1349 (94.4%)	1342 (93.9%)	
	YES	217 (4.1%)	93 (6.2%)		80 (5.6%)	87 (6.1%)	
Estradiol				-0.06			-0.05
	NO	4810 (91.8%)	1413 (93.5%)		1320 (92.4%)	1339 (93.7%)	
	YES	430 (8.2%)	99 (6.5%)		109 (7.6%)	90 (6.3%)	
Medroxyprogesterone				-0.03			-0.05
	NO	5195 (99.1%)	1503 (99.4%)		1413 (98.9%)	1420 (99.4%)	
	YES	45 (0.9%)	9 (0.6%)		16 (1.1%)	9 (0.6%)	

Variable	Value	Venlafaxine	Duloxetine	Std. diff.	Venlafaxine PS sample	Duloxetine PS sample	Std. diff. PS sample
Hydroxyprogesterone				0			0
	NO	5240 (100.0%)	1512 (100.0%)		1429 (100.0%)	1429 (100.0%)	
Progesterone				-0.05			-0.04
	NO	5081 (97.0%)	1479 (97.8%)		1391 (97.3%)	1400 (98.0%)	
	YES	159 (3.0%)	33 (2.2%)		38 (2.7%)	29 (2.0%)	
Danazol				0			0
	NO	5240 (100.0%)	1512 (100.0%)		1429 (100.0%)	1429 (100.0%)	
	YES	<5 (0%)	<5 (0%)				
Betamethasone				0.01			0.00
	NO	5189 (99.0%)	1495 (98.9%)		1412 (98.8%)	1412 (98.8%)	
	YES	51 (1.0%)	17 (1.1%)		17 (1.2%)	17 (1.2%)	
Prednisone				-0.02			0
	NO	5239 (100.0%)	1512 (100.0%)		1429 (100.0%)	1429 (100.0%)	
	YES	<5 (0%)	<5 (0%)				
Thyroid				0.08			-0.03
	NO	4974 (94.9%)	1407 (93.1%)		1318 (92.2%)	1330 (93.1%)	
	YES	266 (5.1%)	105 (6.9%)		111 (7.8%)	99 (6.9%)	
Antithyroid				-0.02			-0.05
	NO	5233 (99.9%)	1511 (99.9%)		1425 (99.7%)	1428 (99.9%)	
	YES	7 (0.1%)	<5 (0%)		<5 (0%)	<5 (0%)	

Variable	Value	Venlafaxine	Duloxetine	Std. diff.	Venlafaxine PS sample	Duloxetine PS sample	Std. diff. PS sample
Propylthiouracil				-0.03			-0.04
	NO	5237 (99.9%)	1512 (100.0%)		1428 (99.9%)	1429 (100.0%)	
	YES	<5 (0%)	<5 (0%)		<5 (0%)	<5 (0%)	
Methimazole				-0.00			-0.04
	NO	5236 (99.9%)	1511 (99.9%)		1426 (99.8%)	1428 (99.9%)	
	YES	<5 (0%)	<5 (0%)		<5 (0%)	<5 (0%)	
NSAID				0.13			0.03
	NO	4673 (89.2%)	1284 (84.9%)		1240 (86.8%)	1225 (85.7%)	
	YES	567 (10.8%)	228 (15.1%)		189 (13.2%)	204 (14.3%)	
Opioids				0.25			0.02
	NO	4799 (91.6%)	1262 (83.5%)		1208 (84.5%)	1200 (84.0%)	
	YES	441 (8.4%)	250 (16.5%)		221 (15.5%)	229 (16.0%)	
Triptans				0.08			0.04
	NO	5047 (96.3%)	1431 (94.6%)		1368 (95.7%)	1355 (94.8%)	
	YES	193 (3.7%)	81 (5.4%)		61 (4.3%)	74 (5.2%)	
Antiepileptics				0.21			0.03
	NO	4822 (92.0%)	1290 (85.3%)		1244 (87.1%)	1228 (85.9%)	
	YES	418 (8.0%)	222 (14.7%)		185 (12.9%)	201 (14.1%)	
Antipsychotics				0.10			0.02
	NO	4802 (91.6%)	1341 (88.7%)		1278 (89.4%)	1267 (88.7%)	
	YES	438 (8.4%)	171 (11.3%)		151 (10.6%)	162 (11.3%)	

Variable	Value	Venlafaxine	Duloxetine	Std. diff.	Venlafaxine PS sample	Duloxetine PS sample	Std. diff. PS sample
Anxiolytics				0.12			0.03
	NO	4385 (83.7%)	1193 (78.9%)		1148 (80.3%)	1133 (79.3%)	
	YES	855 (16.3%)	319 (21.1%)		281 (19.7%)	296 (20.7%)	
Corticosteroid (combination)				0.09			0.00
	NO	4871 (93.0%)	1367 (90.4%)		1292 (90.4%)	1290 (90.3%)	
	YES	369 (7.0%)	145 (9.6%)		137 (9.6%)	139 (9.7%)	
Fluticasone				0.00			0.01
	NO	5220 (99.6%)	1506 (99.6%)		1424 (99.7%)	1423 (99.6%)	
	YES	20 (0.4%)	6 (0.4%)		5 (0.3%)	6 (0.4%)	
Progesterone (combination)				-0.06			-0.05
	NO	5047 (96.3%)	1471 (97.3%)		1380 (96.6%)	1392 (97.4%)	
	YES	193 (3.7%)	41 (2.7%)		49 (3.4%)	37 (2.6%)	
Antithyroid (combination)				-0.02			-0.05
	NO	5233 (99.9%)	1511 (99.9%)		1425 (99.7%)	1428 (99.9%)	
	YES	7 (0.1%)	<5 (0%)		<5 (0%)	<5 (0%)	
SSRI				-0.56			-0.55
	NO	4530 (86.5%)	1512 (100.0%)		1244 (87.1%)	1429 (100.0%)	
	YES	710 (13.5%)	<5 (0%)		185 (12.9%)	<5 (0%)	

Variable	Value	Venlafaxine	Duloxetine	Std. diff.	Venlafaxine PS sample	Duloxetine PS sample	Std. diff. PS sample
venlafaxine				.			.
	NO	<5 (0%)	1512 (100.0%)		<5 (0%)	1429 (100.0%)	
	YES	5240 (100.0%)	<5 (0%)		1429 (100.0%)	<5 (0%)	

Numbers show number of pregnancies (percentage) or median (interquartile range).
Propensity score base on: data source (Sweden/Denmark), age (grouped), education grouped, household income, year (grouped), psychiatric hospital, psychiatric outpatient, smoking, previous spontaneous abortion, previous stillbirth, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, renal failure, depression, affective disorder, anxiety or phobia, severe stress reaction, diabetic peripheral neuropathic pain, glucose lowering, antihypertensive, fluconazole, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination)

10.2.1.4. Background characteristics. Analyses: Malformation. Comparison group: duloxetine discontinuers.

Variable	Value	Duloxetine discontinuers	Duloxetine	Std. diff.	Duloxetine discontinuers PS sample	Duloxetine PS sample	Std. diff. PS sample
Age, continuous (mean)				0.11			0.04
		30.3 (26.6; 34.3)	30.8 (27.2; 35.1)		30.5 (26.7; 34.7)	30.7 (27.2; 35.0)	
Age, grouped				0.07			0.05
	18-24 years	470 (16.3%)	231 (15.3%)		230 (16.0%)	222 (15.5%)	
	25-29 years	914 (31.8%)	447 (29.6%)		435 (30.3%)	427 (29.8%)	
	30-34 years	710 (24.7%)	379 (25.1%)		336 (23.4%)	359 (25.0%)	
	35-60 years	782 (27.2%)	455 (30.1%)		434 (30.2%)	426 (29.7%)	

Variable	Value	Duloxetine discontinuers	Duloxetine	Std. diff.	Duloxetine discontinuers PS sample	Duloxetine PS sample	Std. diff. PS sample
BMI, continuous (mean)				0.04			-0.02
		25.0 (22.2; 29.7)	25.4 (22.3; 30.0)		25.5 (22.5; 29.8)	25.4 (22.3; 29.8)	
BMI, grouped				0.08			0.06
	BMI <21	370 (13.8%)	210 (14.9%)		177 (12.8%)	206 (14.9%)	
	BMI 21-26<	1154 (43.0%)	555 (39.3%)		577 (41.6%)	545 (39.6%)	
	BMI 26-30<	516 (19.2%)	294 (20.8%)		295 (21.3%)	287 (20.8%)	
	BMI >=30	644 (24.0%)	353 (25.0%)		337 (24.3%)	340 (24.7%)	
Household income				0.05			0.05
	income quartile1	1051 (36.7%)	569 (37.8%)		560 (39.0%)	549 (38.3%)	
	income quartile2	815 (28.5%)	391 (25.9%)		346 (24.1%)	367 (25.6%)	
	income quartile3	597 (20.9%)	317 (21.0%)		317 (22.1%)	300 (20.9%)	
	income quartile4	399 (13.9%)	230 (15.3%)		212 (14.8%)	218 (15.2%)	
Education				0.06			0.05
	< 11 years	714 (25.0%)	341 (22.7%)		301 (21.0%)	325 (22.7%)	
	11-15 years	1452 (50.8%)	806 (53.7%)		791 (55.1%)	770 (53.7%)	
	>16 years	692 (24.2%)	355 (23.6%)		343 (23.9%)	339 (23.6%)	

Variable	Value	Duloxetine discontinuers	Duloxetine	Std. diff.	Duloxetine discontinuers PS sample	Duloxetine PS sample	Std. diff. PS sample
Smoking				-0.01			0.02
	NO	2184 (79.1%)	1152 (79.3%)		1150 (80.1%)	1138 (79.4%)	
	YES	578 (20.9%)	301 (20.7%)		285 (19.9%)	296 (20.6%)	
Data source				0.07			0.01
	0	1055 (36.7%)	502 (33.2%)		485 (33.8%)	479 (33.4%)	
	1	1821 (63.3%)	1010 (66.8%)		950 (66.2%)	955 (66.6%)	
Previous stillbirth				-0.03			0.01
	0	2859 (99.4%)	1506 (99.6%)		1430 (99.7%)	1428 (99.6%)	
	1	17 (0.6%)	6 (0.4%)		5 (0.3%)	6 (0.4%)	
Parity				0.06			0.09
	0	1429 (49.8%)	711 (47.2%)		714 (49.8%)	661 (46.3%)	
	1	734 (25.6%)	401 (26.6%)		370 (25.8%)	388 (27.2%)	
	2	451 (15.7%)	254 (16.9%)		229 (16.0%)	244 (17.1%)	
	>2	253 (8.8%)	140 (9.3%)		120 (8.4%)	135 (9.5%)	
Prev. spontaneous abortions				0.07			0.03
	0	2205 (76.7%)	1186 (78.4%)		1134 (79.0%)	1122 (78.2%)	
	1	511 (17.8%)	238 (15.7%)		218 (15.2%)	228 (15.9%)	
	2+	160 (5.6%)	88 (5.8%)		83 (5.8%)	84 (5.9%)	

Variable	Value	Duloxetine discontinuers	Duloxetine	Std. diff.	Duloxetine discontinuers PS sample	Duloxetine PS sample	Std. diff. PS sample
Outpatient visits, continuous				-0.06			-0.09
		0.0 (0.0; 0.0)	0.0 (0.0; 0.0)		0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	
Outpatient visits, grouped				0.08			0.13
	0	2583 (89.8%)	1390 (91.9%)		1284 (89.5%)	1322 (92.2%)	
	1	198 (6.9%)	89 (5.9%)		95 (6.6%)	82 (5.7%)	
	>1	95 (3.3%)	33 (2.2%)		56 (3.9%)	30 (2.1%)	
Hospital, continuous				0.03			-0.02
		0.0 (0.0; 0.0)	0.0 (0.0; 0.0)		0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	
Hospital, grouped				0.07			0.08
	0	2495 (86.8%)	1286 (85.1%)		1242 (86.6%)	1228 (85.6%)	
	1	243 (8.4%)	152 (10.1%)		111 (7.7%)	140 (9.8%)	
	>1	138 (4.8%)	74 (4.9%)		82 (5.7%)	66 (4.6%)	
Emergency depart., continuous				-0.03			-0.02
		0.0 (0.0; 0.0)	0.0 (0.0; 0.0)		0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	
Emergency depart., grouped				0.05			0.00
	0	2696 (93.7%)	1430 (94.6%)		1350 (94.1%)	1354 (94.4%)	
	1	113 (3.9%)	51 (3.4%)		49 (3.4%)	50 (3.5%)	
	>1	67 (2.3%)	31 (2.1%)		36 (2.5%)	30 (2.1%)	

Variable	Value	Duloxetine discontinuers	Duloxetine	Std. diff.	Duloxetine discontinuers PS sample	Duloxetine PS sample	Std. diff. PS sample
Psychiatric outpatient, continuous				0.04			-0.02
		0.0 (0.0; 1.0)	0.0 (0.0; 1.0)		0.0 (0.0; 1.0)	0.0 (0.0; 1.0)	
Psychiatric outpatient, grouped				0.05			0.04
	0	2055 (71.5%)	1043 (69.0%)		1019 (71.0%)	994 (69.3%)	
	1+	821 (28.5%)	469 (31.0%)		416 (29.0%)	440 (30.7%)	
Psychiatric hospital, continuous				0.07			0.01
		0.0 (0.0; 0.0)	0.0 (0.0; 0.0)		0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	
Psychiatric hospital, grouped				0.06			-0.01
	0	2731 (95.0%)	1416 (93.7%)		1345 (93.7%)	1348 (94.0%)	
	1+	145 (5.0%)	96 (6.3%)		90 (6.3%)	86 (6.0%)	
Gestational diabetes during index pregnancy				0.02			-0.01
	0	2725 (94.7%)	1424 (94.2%)		1351 (94.1%)	1353 (94.4%)	
	1	151 (5.3%)	88 (5.8%)		84 (5.9%)	81 (5.6%)	
Diabetes				0.01			0.03
	NO	2805 (97.5%)	1472 (97.4%)		1405 (97.9%)	1398 (97.5%)	
	YES	71 (2.5%)	40 (2.6%)		30 (2.1%)	36 (2.5%)	

Variable	Value	Duloxetine discontinuers	Duloxetine	Std. diff.	Duloxetine discontinuers PS sample	Duloxetine PS sample	Std. diff. PS sample
Hyper or hypothyroidism				0.08			0.01
	NO	2741 (95.3%)	1412 (93.4%)		1343 (93.6%)	1339 (93.4%)	
	YES	135 (4.7%)	100 (6.6%)		92 (6.4%)	95 (6.6%)	
Hypertension				0.02			-0.02
	NO	2855 (99.3%)	1498 (99.1%)		1420 (99.0%)	1422 (99.2%)	
	YES	21 (0.7%)	14 (0.9%)		15 (1.0%)	12 (0.8%)	
Obesity				0.02			0.01
	NO	2676 (93.0%)	1401 (92.7%)		1333 (92.9%)	1328 (92.6%)	
	YES	200 (7.0%)	111 (7.3%)		102 (7.1%)	106 (7.4%)	
Depression				0.13			0.01
	NO	2064 (71.8%)	995 (65.8%)		958 (66.8%)	952 (66.4%)	
	YES	812 (28.2%)	517 (34.2%)		477 (33.2%)	482 (33.6%)	
Affective disorder				0.04			0.02
	NO	2793 (97.1%)	1459 (96.5%)		1393 (97.1%)	1386 (96.7%)	
	YES	83 (2.9%)	53 (3.5%)		42 (2.9%)	48 (3.3%)	
Anxiety or phobia				0.04			0.04
	NO	2549 (88.6%)	1319 (87.2%)		1273 (88.7%)	1254 (87.4%)	
	YES	327 (11.4%)	193 (12.8%)		162 (11.3%)	180 (12.6%)	

Variable	Value	Duloxetine discontinuers	Duloxetine	Std. diff.	Duloxetine discontinuers PS sample	Duloxetine PS sample	Std. diff. PS sample
Severe stress reaction				0.05			0.03
	NO	2598 (90.3%)	1341 (88.7%)		1298 (90.5%)	1283 (89.5%)	
	YES	278 (9.7%)	171 (11.3%)		137 (9.5%)	151 (10.5%)	
Stress urinary incontinence				0			0
	NO	2876 (100.0%)	1512 (100.0%)		1435 (100.0%)	1434 (100.0%)	
Renal failure				-0.00			0.00
	NO	2874 (99.9%)	1511 (99.9%)		1434 (99.9%)	1433 (99.9%)	
	YES	<5 (0%)	<5 (0%)		<5 (0%)	<5 (0%)	
Triamcinolone				0.02			0.04
	NO	2873 (99.9%)	1509 (99.8%)		1434 (99.9%)	1431 (99.8%)	
	YES	<5 (0%)	<5 (0%)		<5 (0%)	<5 (0%)	
Dexamethasone				0			0
	NO	2876 (100.0%)	1512 (100.0%)		1435 (100.0%)	1434 (100.0%)	
	YES	<5 (0%)	<5 (0%)				
Cortisone				0.05			0.04
	NO	2859 (99.4%)	1497 (99.0%)		1425 (99.3%)	1419 (99.0%)	
	YES	17 (0.6%)	15 (1.0%)		10 (0.7%)	15 (1.0%)	
Prednisolone				-0.02			-0.01
	NO	2825 (98.2%)	1489 (98.5%)		1410 (98.3%)	1411 (98.4%)	
	YES	51 (1.8%)	23 (1.5%)		25 (1.7%)	23 (1.6%)	

Variable	Value	Duloxetine discontinuers	Duloxetine	Std. diff.	Duloxetine discontinuers PS sample	Duloxetine PS sample	Std. diff. PS sample
Budesonide				0.06			0.06
	NO	2874 (99.9%)	1507 (99.7%)		1434 (99.9%)	1429 (99.7%)	
	YES	<5 (0%)	5 (0.3%)		<5 (0%)	5 (0.3%)	
Glucose lowering				-0.02			0.02
	NO	2812 (97.8%)	1483 (98.1%)		1411 (98.3%)	1407 (98.1%)	
	YES	64 (2.2%)	29 (1.9%)		24 (1.7%)	27 (1.9%)	
Antihypertensive				0.08			0.01
	NO	2779 (96.6%)	1438 (95.1%)		1368 (95.3%)	1364 (95.1%)	
	YES	97 (3.4%)	74 (4.9%)		67 (4.7%)	70 (4.9%)	
Fluconazole				-0.01			0.06
	NO	2767 (96.2%)	1458 (96.4%)		1400 (97.6%)	1384 (96.5%)	
	YES	109 (3.8%)	54 (3.6%)		35 (2.4%)	50 (3.5%)	
Mometasone				0.03			0.02
	NO	2721 (94.6%)	1419 (93.8%)		1354 (94.4%)	1345 (93.8%)	
	YES	155 (5.4%)	93 (6.2%)		81 (5.6%)	89 (6.2%)	
Estradiol				-0.01			-0.02
	NO	2677 (93.1%)	1413 (93.5%)		1337 (93.2%)	1343 (93.7%)	
	YES	199 (6.9%)	99 (6.5%)		98 (6.8%)	91 (6.3%)	
Medroxyprogesterone				-0.02			0.03
	NO	2855 (99.3%)	1503 (99.4%)		1429 (99.6%)	1425 (99.4%)	
	YES	21 (0.7%)	9 (0.6%)		6 (0.4%)	9 (0.6%)	

Variable	Value	Duloxetine discontinuers	Duloxetine	Std. diff.	Duloxetine discontinuers PS sample	Duloxetine PS sample	Std. diff. PS sample
Hydroxyprogesterone				0			0
	NO	2876 (100.0%)	1512 (100.0%)		1435 (100.0%)	1434 (100.0%)	
Progesterone				-0.06			-0.06
	NO	2787 (96.9%)	1479 (97.8%)		1392 (97.0%)	1405 (98.0%)	
	YES	89 (3.1%)	33 (2.2%)		43 (3.0%)	29 (2.0%)	
Danazol				0			0
	NO	2876 (100.0%)	1512 (100.0%)		1435 (100.0%)	1434 (100.0%)	
	YES	<5 (0%)	<5 (0%)				
Betamethasone				-0.00			-0.01
	NO	2843 (98.9%)	1495 (98.9%)		1417 (98.7%)	1417 (98.8%)	
	YES	33 (1.1%)	17 (1.1%)		18 (1.3%)	17 (1.2%)	
Prednisone				-0.03			-0.04
	NO	2875 (100.0%)	1512 (100.0%)		1434 (99.9%)	1434 (100.0%)	
	YES	<5 (0%)	<5 (0%)		<5 (0%)	<5 (0%)	
Thyroid				0.07			-0.01
	NO	2725 (94.7%)	1407 (93.1%)		1332 (92.8%)	1333 (93.0%)	
	YES	151 (5.3%)	105 (6.9%)		103 (7.2%)	101 (7.0%)	
Antithyroid				-0.03			-0.04
	NO	2871 (99.8%)	1511 (99.9%)		1432 (99.8%)	1433 (99.9%)	
	YES	5 (0.2%)	<5 (0%)		<5 (0%)	<5 (0%)	

Variable	Value	Duloxetine discontinuers	Duloxetine	Std. diff.	Duloxetine discontinuers PS sample	Duloxetine PS sample	Std. diff. PS sample
Propylthiouracil				-0.04			-0.04
	NO	2874 (99.9%)	1512 (100.0%)		1434 (99.9%)	1434 (100.0%)	
	YES	<5 (0%)	<5 (0%)		<5 (0%)	<5 (0%)	
Methimazole				-0.02			-0.02
	NO	2872 (99.9%)	1511 (99.9%)		1433 (99.9%)	1433 (99.9%)	
	YES	<5 (0%)	<5 (0%)		<5 (0%)	<5 (0%)	
NSAID				0.05			0.02
	NO	2495 (86.8%)	1284 (84.9%)		1237 (86.2%)	1224 (85.4%)	
	YES	381 (13.2%)	228 (15.1%)		198 (13.8%)	210 (14.6%)	
Opioids				0.05			0.04
	NO	2455 (85.4%)	1262 (83.5%)		1220 (85.0%)	1197 (83.5%)	
	YES	421 (14.6%)	250 (16.5%)		215 (15.0%)	237 (16.5%)	
Triptans				0.08			0.02
	NO	2767 (96.2%)	1431 (94.6%)		1361 (94.8%)	1355 (94.5%)	
	YES	109 (3.8%)	81 (5.4%)		74 (5.2%)	79 (5.5%)	
Antiepileptics				0.16			0.02
	NO	2603 (90.5%)	1290 (85.3%)		1243 (86.6%)	1230 (85.8%)	
	YES	273 (9.5%)	222 (14.7%)		192 (13.4%)	204 (14.2%)	

Variable	Value	Duloxetine discontinuers	Duloxetine	Std. diff.	Duloxetine discontinuers PS sample	Duloxetine PS sample	Std. diff. PS sample
Antipsychotics				0.11			0.00
	NO	2647 (92.0%)	1341 (88.7%)		1274 (88.8%)	1273 (88.8%)	
	YES	229 (8.0%)	171 (11.3%)		161 (11.2%)	161 (11.2%)	
Anxiolytics				0.16			0.01
	NO	2443 (84.9%)	1193 (78.9%)		1145 (79.8%)	1136 (79.2%)	
	YES	433 (15.1%)	319 (21.1%)		290 (20.2%)	298 (20.8%)	
Corticosteroid (combination)				0.03			0.02
	NO	2623 (91.2%)	1367 (90.4%)		1303 (90.8%)	1293 (90.2%)	
	YES	253 (8.8%)	145 (9.6%)		132 (9.2%)	141 (9.8%)	
Fluticasone				0.01			0.02
	NO	2867 (99.7%)	1506 (99.6%)		1431 (99.7%)	1428 (99.6%)	
	YES	9 (0.3%)	6 (0.4%)		<5 (0%)	6 (0.4%)	
Progesterone (combination)				-0.05			-0.04
	NO	2773 (96.4%)	1471 (97.3%)		1389 (96.8%)	1397 (97.4%)	
	YES	103 (3.6%)	41 (2.7%)		46 (3.2%)	37 (2.6%)	
Antithyroid (combination)				-0.03			-0.04
	NO	2871 (99.8%)	1511 (99.9%)		1432 (99.8%)	1433 (99.9%)	
	YES	5 (0.2%)	<5 (0%)		<5 (0%)	<5 (0%)	

Variable	Value	Duloxetine discontinuers	Duloxetine	Std. diff.	Duloxetine discontinuers PS sample	Duloxetine PS sample	Std. diff. PS sample
SSRI				-0.71			-0.73
	NO	2297 (79.9%)	1512 (100.0%)		1133 (79.0%)	1434 (100.0%)	
	YES	579 (20.1%)	<5 (0%)		302 (21.0%)	<5 (0%)	
venlafaxine				-0.25			-0.27
	NO	2788 (96.9%)	1512 (100.0%)		1386 (96.6%)	1434 (100.0%)	
	YES	88 (3.1%)	<5 (0%)		49 (3.4%)	<5 (0%)	

Numbers show number of pregnancies (percentage) or median (interquartile range).

Propensity score base on: data source (Sweden/Denmark), age (grouped), education grouped, household income, year (grouped), psychiatric hospital, psychiatric outpatient, smoking, previous spontaneous abortion, previous stillbirth, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, renal failure, depression, affective disorder, anxiety or phobia, severe stress reaction, diabetic peripheral neuropathic pain, glucose lowering, antihypertensive, fluconazole, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination)

10.3. Outcome data

Table 10.1 Number of exposed and number of events for each cohort. Exposure definition: ≥1 redeemed prescription

Exposure cohort	Duloxetine exposed (events)	SSRI exposed (events)	Venlafaxine exposed (events)	Duloxetine discontinuers (events)	Duloxetine non-exposed (events)
Major malformation	1,512 (65)	39,959 (1,777)	5,240 (236)	2,876 (142)	2,074,652 (80,695)
Minor malformation	1,512 (66)	39,959 (1,385)	5,240 (203)	2,876 (98)	2,074,652 (64,528)
Spontaneous abortion	1,212 (145)	28,345 (2,900)	4,908 (497)	1,418 (168)	1,018,745 (106,309)
Elective abortion	1,212 (406)	28,345 (6,972)	4,908 (1,529)	1,418 (331)	1,018,745 (153,691)
Stillbirth	1,668 (5)	54,797 (252)	6,008 (44)	2,817 (10)	2,130,773 (7,694)
Preterm birth - early exposure	1,589 (183)	46,726 (4,226)	5,642 (717)	2,839 (272)	2,080,880 (127,096)
Preterm birth - late exposure	450 (73)	37,423 (3,241)	3,234 (515)	3,772 (363)	2,082,019 (127,206)
Small for gestational age - without malformation - early exposure	1,516 (146)	44,569 (4,509)	5,375 (502)	2,691 (244)	1,996,843 (188,122)
Small for gestational age - without malformation - late exposure	427 (35)	35,821 (3,631)	3,078 (262)	3,580 (335)	1,997,932 (188,233)
Small for gestational age - with malformation - early exposure	73 (11)	2,155 (275)	267 (33)	148 (13)	83,817 (11,043)
Small for gestational age - with malformation - late exposure	23 (<5)	1,600 (211)	155 (16)	192 (19)	83,867 (11,050)

Table 10.2 Number of events per thousand pregnancies, with 95% confidence intervals, for each cohort.

Exposure cohort	Duloxetine exposed	Duloxetine non-exposed	SSRI exposed	Venlafaxine exposed	Duloxetine discontinuers
Major malformation	43 (32.8;53.2)	38.9 (38.6;39.2)	44.5 (42.4;46.5)	45 (39.4;50.7)	49.4 (41.5;57.3)
Minor malformation	43.7 (33.4;53.9)	31.1 (30.9;31.3)	34.7 (32.9;36.5)	38.7 (33.5;44)	34.1 (27.4;40.7)
Spontaneous abortion	119.6 (101.4;137.9)	104.4 (103.8;104.9)	102.3 (98.8;105.8)	101.3 (92.8;109.7)	118.5 (101.7;135.3)
Elective abortion	335 (308.4;361.6)	150.9 (150.2;151.6)	246 (241;251)	311.5 (298.6;324.5)	233.4 (211.4;255.4)
Stillbirth	3 (0.4;5.6)	3.6 (3.5;3.7)	4.6 (4;5.2)	7.3 (5.2;9.5)	3.5 (1.4;5.7)
Preterm birth - early exposure	115.2 (99.5;130.9)	61.1 (60.8;61.4)	90.4 (87.8;93)	127.1 (118.4;135.8)	95.8 (85;106.6)
Preterm birth - late exposure	162.2 (128.2;196.3)	61.1 (60.8;61.4)	86.6 (83.8;89.5)	159.2 (146.6;171.9)	96.2 (86.8;105.6)
SGA - without malformation - early exposure	96.3 (81.5;111.2)	94.2 (93.8;94.6)	101.2 (98.4;104)	93.4 (85.6;101.2)	90.7 (79.8;101.5)
SGA - without malformation - late exposure	82 (55.9;108)	94.2 (93.8;94.6)	101.4 (98.2;104.5)	85.1 (75.3;95)	93.6 (84;103.1)
SGA - with malformation - early exposure	150.7 (68.6;232.7)	131.8 (129.5;134)	127.6 (113.5;141.7)	123.6 (84.1;163.1)	87.8 (42.2;133.4)
SGA - with malformation - late exposure	N/A	131.8 (129.5;134)	131.9 (115.3;148.5)	103.2 (55.3;151.1)	99 (56.7;141.2)
SGA - All - early exposure	98.8 (84.1;113.5)	95.7 (95.3;96.1)	102.4 (99.6;105.1)	94.8 (87.2;102.5)	90.5 (80;101.1)
SGA - All - late exposure	86.7 (60.7;112.7)	95.7 (95.3;96.1)	102.7 (99.6;105.7)	86 (76.3;95.6)	93.8 (84.5;103.2)

Table continued

Exposure cohort	Duloxetine exposed	Duloxetine non-exposed	SSRI exposed	Venlafaxine exposed	Duloxetine discontinuers
Major malformation: Heart	16.5 (10.1;23)	13.3 (13.1;13.4)	17.7 (16.4;19)	17.6 (14;21.1)	14.6 (10.2;19)
Major malformation: Digestive system	16.5 (10.1;23)	9.3 (9.2;9.4)	11.5 (10.5;12.6)	13.2 (10.1;16.3)	11.1 (7.3;15)
Major malformation: Ear Face or Neck	4 (0.8;7.1)	2.4 (2.3;2.4)	2.5 (2;3)	1.9 (0.7;3.1)	N/A
Major malformation: Eye	3.3 (0.4;6.2)	2.6 (2.5;2.7)	2.5 (2;2.9)	2.5 (1.1;3.8)	5.6 (2.8;8.3)
Major malformation: Genital	4 (0.8;7.1)	4.3 (4.2;4.4)	4.5 (3.8;5.2)	2.5 (1.1;3.8)	5.2 (2.6;7.8)
Major malformation: Abdominal wall	N/A	0.3 (0.2;0.3)	0.5 (0.3;0.7)	N/A	N/A
Major malformation: Limp	15.2 (9;21.4)	18.7 (18.5;18.8)	20.4 (19;21.8)	22.7 (18.7;26.7)	21.9 (16.6;27.3)
Major malformation: Nervous system	N/A	1.2 (1.2;1.3)	1.4 (1;1.7)	1.9 (0.7;3.1)	2.8 (0.9;4.7)
Major malformation: Oro-facial clefts	N/A	1.7 (1.6;1.8)	1.8 (1.4;2.2)	2.5 (1.1;3.8)	1.7 (0.2;3.3)
Major malformation: Respiratory	N/A	1.3 (1.3;1.4)	1.6 (1.2;2)	1.5 (0.5;2.6)	1.7 (0.2;3.3)
Major malformation: Urinary	5.3 (1.6;8.9)	3.6 (3.5;3.7)	3.7 (3.1;4.3)	2.9 (1.4;4.3)	3.5 (1.3;5.6)
Major malformation: Other	9.3 (4.4;14.1)	4.8 (4.7;4.9)	5.9 (5.1;6.6)	4.2 (2.4;5.9)	4.5 (2.1;7)

Numbers show events per 1000 pregnancies (95%CI). Exposure definition: ≥1 redeemed prescription.

95% confidence interval based on Wald and binomial distribution. For spontaneous and elective abortion: number of events is shown per 1000 pregnancies in this table, while the main analyses are based on cox regression and events during duration of pregnancy. N/A: rates cannot be presented due to <5 events.

10.4. Time to event

The tables below are presenting the distribution of the duration of pregnancies, for elective abortions and preterm deliveries.

10.4.1. Duration of pregnancy for elective abortions

Table 10.3 Duration of pregnancy for elective abortions stratified for exposure groups

	Duration (gestational age in days)				
Exposure group	**Median**	**5th percentile**	**25th percentile**	**75th percentile**	**95th Percentile**
Duloxetine non-exposed	56.0	38	48	66	88
Duloxetine	55.5	40	48	63	80
SSRI	56.0	40	48	65	83
Venlafaxine	56.0	35	49	66	83
Duloxetine discontinuers	55.0	37	48	67	82

10.4.2. Duration of pregnancy for preterm deliveries

Table 10.4 Duration of pregnancy for preterm deliveries stratified for exposure periods and exposure groups

		Duration (gestational age in days)				
Period	**Exposure group**	**Median**	**5th percentile**	**25th percentile**	**75th percentile**	**95th Percentile**
Early	duloxetine non-exposed	248	195	234	254	258
Early	Duloxetine	247	202	238	254	258
Early	SSRI	248	198	235	254	258
Early	Venlafaxine	247	202	238	254	258
Early	duloxetine discontinuers	249	191	237	254	258
Late	duloxetine non-exposed	248	195	234	254	258
Late	Duloxetine	249	219	241	255	258
Late	SSRI	249	211	239	255	258
Late	Venlafaxine	248	212	240	254	258
Late	duloxetine discontinuers	248	191	237	254	258

Table 10.5 Number of births (percentage) per gestational week stratified for exposure group - early exposure window

Exposure group	week 20-25	week26	week27	week28	week29	week30	week31	week32	week33	week34
Duloxetine exposed	<5	<5	<5	<5	<5	<5	13 (1%)	6 (0%)	12 (1%)	29 (2%)
Duloxetine Non-exposed	3,197 (0%)	1,455 (0%)	1,789 (0%)	2,208 (0%)	2,703 (0%)	3,598 (0%)	4,709 (0%)	6,851 (0%)	10,213 (0%)	16,730 (1%)
SSRI Exposed	85 (0%)	47 (0%)	61 (0%)	58 (0%)	84 (0%)	118 (0%)	152 (0%)	251 (1%)	324 (1%)	559 (1%)
Venlafaxine exposed	10 (0%)	<5	11 (0%)	11 (0%)	10 (0%)	19 (0%)	17 (0%)	44 (1%)	52 (1%)	109 (2%)
Duloxetine discontinuers	6 (0%)	<5	10 (0%)	<5	<5	9 (0%)	6 (0%)	12 (0%)	17 (1%)	36 (1%)

Table continued

Exposure	week35	week36	week37	week38	week39	week40	week41	week42	week43-45
Duloxetine exposed	40 (3%)	69 (4%)	191 (12%)	349 (22%)	369 (23%)	292 (18%)	164 (10%)	41 (3%)	<5
Duloxetine Non-exposed	26,009 (1%)	47,737 (2%)	112,488 (5%)	293,443 (14%)	470,044 (23%)	572,067 (27%)	386,028 (19%)	117,836 (6%)	2,773 (0%)
SSRI exposed	906 (2%)	1,607 (3%)	3,803 (8%)	8,873 (19%)	11,699 (25%)	11,058 (24%)	5,780 (12%)	1,503 (3%)	26 (0%)
Venlafaxine exposed	173 (3%)	260 (5%)	632 (11%)	1,167 (21%)	1,363 (24%)	1,122 (20%)	514 (9%)	154 (3%)	<5
Duloxetine discontinuers	61 (2%)	106 (4%)	231 (8%)	535 (19%)	662 (23%)	617 (22%)	404 (14%)	117 (4%)	<5

Exposure definition: ≥1 redeemed prescription

Table 10.6 Number of births (percentage) per gestational week stratified for exposure group - propensity score matched subgroup - early exposure window

Exposure	week20-25	week26	week27	week28	week29	week30	week31	week32	week33	week34
Duloxetine exposed	<5	<5	<5	<5	<5	<5	12 (1%)	<5	11 (1%)	28 (2%)
Duloxetine non-exposed	11 (0%)	<5	8 (0%)	10 (0%)	12 (0%)	19 (0%)	31 (1%)	25 (0%)	30 (0%)	66 (1%)
SSRI exposed	<5	<5	<5	<5	6 (0%)	9 (0%)	14 (0%)	11 (0%)	20 (1%)	35 (1%)
Venlafaxine exposed	<5	<5	<5	<5	<5	<5	8 (1%)	7 (0%)	13 (1%)	28 (2%)
Duloxetine discontinuers	<5	<5	<5	<5	<5	<5	<5	7 (0%)	9 (1%)	23 (2%)

Table continued

Exposure	week35	week36	week37	week38	week39	week40	week41	week42	week43-45
Duloxetine exposed	37 (2%)	64 (4%)	186 (12%)	330 (22%)	350 (23%)	279 (18%)	158 (10%)	37 (2%)	<5
Duloxetine non-exposed	116 (2%)	202 (3%)	476 (8%)	1,068 (18%)	1,418 (23%)	1,405 (23%)	850 (14%)	285 (5%)	7 (0%)
SSRI exposed	65 (2%)	115 (4%)	262 (9%)	597 (20%)	770 (25%)	679 (22%)	347 (11%)	82 (3%)	<5
Venlafaxine exposed	47 (3%)	65 (4%)	176 (12%)	301 (20%)	384 (26%)	297 (20%)	123 (8%)	36 (2%)	<5
Duloxetine discontinuers	31 (2%)	63 (4%)	126 (8%)	289 (19%)	343 (23%)	331 (22%)	208 (14%)	60 (4%)	<5

Exposure definition: ≥1 redeemed prescription

Table 10.7 Number of births (percentage) per gestational week stratified for exposure group - late exposure window

Exposure	week20-25	week26	week27	week28	week29	week30	week31	week32	week33	week34
Duloxetine exposed	<5	<5	<5	<5	<5	<5	<5	<5	<5	13 (3%)
Duloxetine non-exposed	3,200 (0%)	1,455 (0%)	1,791 (0%)	2,212 (0%)	2,703 (0%)	3,601 (0%)	4,718 (0%)	6,855 (0%)	10,220 (0%)	16,746 (1%)
SSRI exposed	18 (0%)	25 (0%)	18 (0%)	32 (0%)	53 (0%)	69 (0%)	111 (0%)	176 (0%)	238 (1%)	453 (1%)
Venlafaxine exposed	<5	<5	8 (0%)	<5	<5	8 (0%)	12 (0%)	29 (1%)	39 (1%)	80 (2%)
Duloxetine discontinuers	9 (0%)	<5	12 (0%)	<5	<5	9 (0%)	15 (0%)	16 (0%)	21 (1%)	49 (1%)

Table continued

Exposure	week35	week36	week37	week38	week39	week40	week41	week42	week43-45
Duloxetine exposed	21 (4%)	30 (6%)	82 (17%)	122 (26%)	116 (24%)	53 (11%)	25 (5%)	<5	<5
Duloxetine non-exposed	26,028 (1%)	47,776 (2%)	112,597 (5%)	293,670 (14%)	470,297 (23%)	572,306 (27%)	386,167 (19%)	117,874 (6%)	2,773 (0%)
SSRI exposed	745 (2%)	1,330 (4%)	3,233 (9%)	7,633 (20%)	9,919 (26%)	8,684 (23%)	3,969 (11%)	933 (2%)	17 (0%)
Venlafaxine exposed	132 (4%)	193 (6%)	457 (14%)	738 (23%)	820 (25%)	516 (16%)	169 (5%)	35 (1%)	<5
Duloxetine discontinuers	80 (2%)	142 (4%)	320 (8%)	732 (19%)	880 (23%)	808 (21%)	518 (14%)	150 (4%)	<5

Exposure definition: ≥1 redeemed prescription

Table 10.8 Number of births (percentage) per gestational week stratified for exposure group - propensity score matched subgroup - late exposure window

Exposure	week20-25	week26	week27	week28	week29	week30	week31	week32	week33	week34
Duloxetine exposed	<5	<5	<5	<5	<5	<5	<5	<5	<5	11 (3%)
Duloxetine non-exposed	<5	<5	<5	<5	<5	<5	<5	10 (1%)	14 (1%)	21 (1%)
SSRI exposed	<5	<5	<5	<5	<5	<5	<5	<5	10 (1%)	9 (1%)
Denlafaxine exposed	<5	<5	<5	<5	<5	<5	<5	<5	<5	13 (3%)
Duloxetine discontinuers	<5	<5	<5	<5	<5	<5	<5	<5	<5	8 (2%)

Table continued

Exposure	week35	week36	week37	week38	week39	week40	week41	week42	week43-45
Duloxetine exposed	14 (3%)	28 (7%)	76 (18%)	104 (25%)	102 (24%)	50 (12%)	22 (5%)	<5	<5
Duloxetine non-exposed	31 (2%)	62 (4%)	164 (10%)	330 (19%)	376 (22%)	345 (20%)	254 (15%)	82 (5%)	<5
SSRI exposed	15 (2%)	34 (4%)	94 (11%)	194 (23%)	229 (27%)	173 (20%)	73 (9%)	12 (1%)	<5
Venlafaxine exposed	11 (3%)	19 (4%)	66 (15%)	106 (25%)	111 (26%)	60 (14%)	25 (6%)	6 (1%)	<5
Duloxetine discontinuers	10 (2%)	14 (3%)	30 (7%)	88 (20%)	127 (28%)	81 (18%)	67 (15%)	18 (4%)	<5

Exposure definition: ≥1 redeemed prescription

10.5. Main results

Below are figures showing the results of the analyses of malformation, spontaneous abortion, elective abortion, stillbirth, SGA, preterm birth and malformation subtypes. Each figure shows the results of the four comparison groups (duloxetine non-exposed , SSRI exposed, venlafaxine/SNRI-exposed, duloxetine discontinuers), and for each comparison group results of the unadjusted, the adjusted and the PS matched analyses are shown.

Corresponding figures for the sensitivity analyses for each outcome are found in the supplementary material:

- Redefinition of exposure to >1 redemption
- Restriction of cohort to first observed pregnancy
- Redefinition of exposure to overlap between redeem prescription and exposure time window (days' supply)
- Inclusion of BMI as covariate

10.5.1. Major malformation

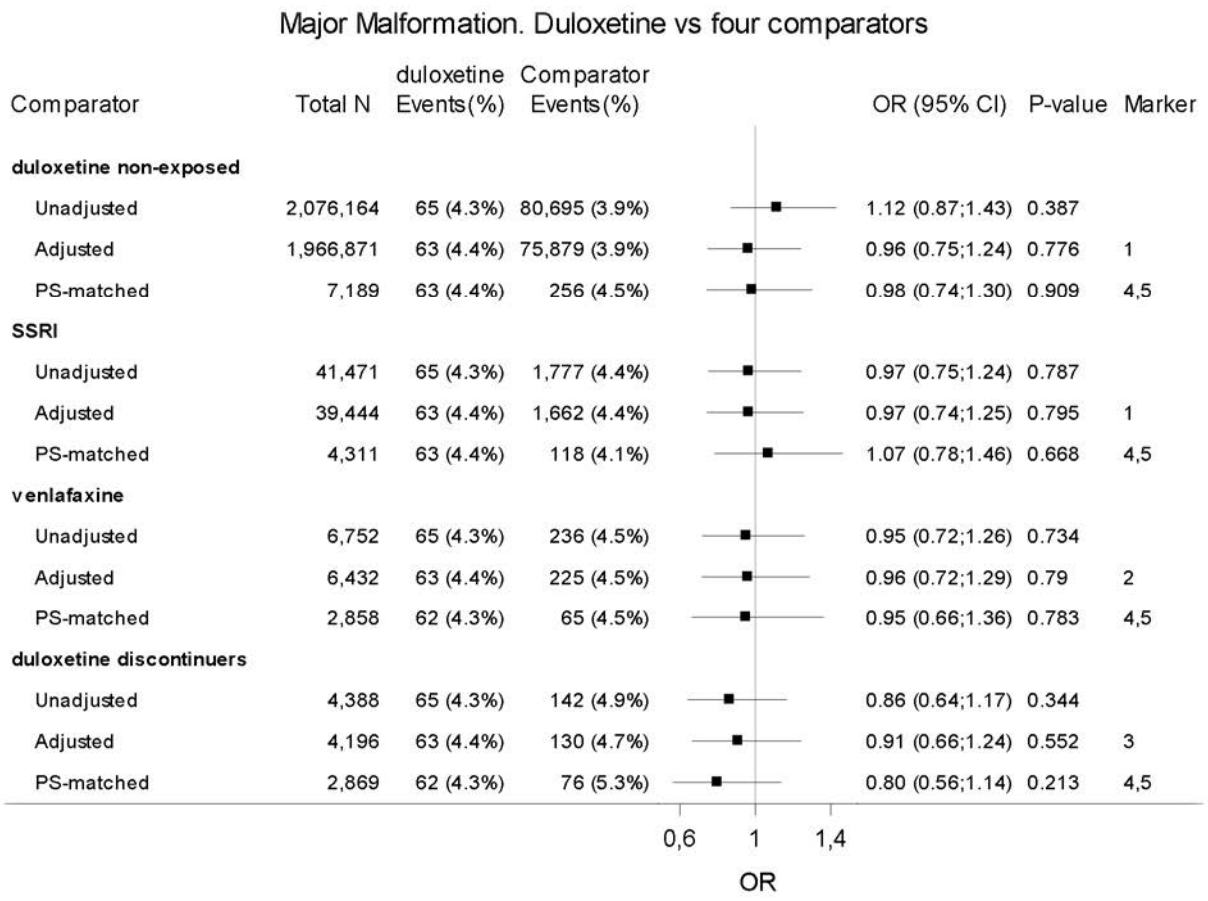
The incidence rate of major malformation was 43.0 per 1,000 (95% CI, 32.8-53.2) in women exposed to duloxetine (65 events among 1,512 exposed women). For the comparator group of duloxetine non-exposed, the incidence rate was 38.9 per 1,000 (95% CI, 38.6-39.2) (corresponding to 80,695 events among 2,074,652 women).

For the other three comparator groups, the incidence rate of major malformation was 44.5 per 1,000 (95% CI 42.4-46.5) in women exposed to SSRI (1,777 events among 39,959 exposed women); 45.0 per 1,000 (95% CI 39.4-50.7) in women exposed to venlafaxine (236 events among 5,240 exposed women) and 49.4 per 1,000 (95% CI 41.5-57.3) in duloxetine discontinuers (142 events among 2,876 exposed women);

Compared to duloxetine non-exposed unadjusted, adjusted and PS-matched analyses OR was 1.12 (95% CI, 0.87-1.43); 0.96 (95% CI, 0.75-1.24) and 0.98 (95% CI, 0.74-1.30), respectively.

Similar results were obtained comparing to the other three comparators SSRI, venlafaxine and duloxetine prior pregnancy, where the OR was 1.07 (95% CI, 0.78-1.46); 0.95 (95% CI, 0.66-1.36) and 0.80 (95% CI, 0.56-1.14) for the PS-matched analyses.

To conclude, all OR point estimates observed – based on unadjusted, adjusted or PS-matched analyses compared to all four references, were close to one, and statistically non-significant, suggesting no increased risk for major congenital malformations across all comparator groups.



Exposure definition: ≥1 redeemed prescription. N: Number of observations in analyses.

OR: Odds ratio for Major Malformation for duloxetine vs. comparators

CI: Wald 95% confidence intervals

Marker 1: Adjusted for data source (Sweden/Denmark), age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, smoking, previous spontaneous abortion, previous stillbirths, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, renal failure, depression, affective, anxiety or phobia, severe stress reaction, diabetic peripheral neuropathic pain, glucose lowering, antihypertensive, fluconazole, estradiol, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination), progesterone (combination), antithyroid (combination).

Marker 2: Adjusted for data source (Sweden/Denmark), age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, smoking, previous spontaneous abortion, previous stillbirths, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, depression, affective, anxiety or phobia, severe stress reaction, glucose lowering, antihypertensive , thyroid, NSAID, opioids, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination), progesterone (combination).

Marker 3: Adjusted for data source (Sweden/Denmark), age (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, smoking, previous spontaneous abortion, previous stillbirths, gestational diabetes during index pregnancy, diabetes, obesity, depression, affective, anxiety or phobia, severe stress reaction, glucose lowering, antihypertensive, estradiol, thyroid, NSAID, opioids, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination), progesterone (combination).

Marker 4: Propensity score based on data source (Sweden/Denmark), age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, smoking, previous spontaneous abortion, previous stillbirths, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, renal failure, depression, affective, anxiety or phobia, severe stress reaction, diabetic peripheral neuropathic pain, glucose lowering, antihypertensive, fluconazole, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination).
Marker 5: Conditional logistic regression

Sensitivity analyses

Overall, the sensitivity analyses support no increased risk of congenital malformations. See Supplementary material, Section 2.1.

10.5.2. Minor malformation

The incidence rate of minor malformation was 43.7 per 1,000 (95% CI, 33.4-53.9) in women exposed to duloxetine (66 events among 1,512 exposed women). For the comparator group of duloxetine non-exposed, the incidence rate was 31.1 per 1,000 (95% CI, 31.3-30.9) (corresponding to 64,528 events among 2,074,652 women).

For the other three comparator groups, the incidence rate of minor malformation was 34.7 per 1,000 (95% CI 32.9-36.5) in women exposed to SSRI (1,385 events among 39,959 exposed women); 38.7 per 1,000 (95% CI 33.5-44.0) in women exposed to venlafaxine (203 events among 5,240 exposed women) and 34.1 per 1,000 (95% CI 27.4-40.7) in duloxetine discontinuers (98 events among 2,876 exposed women).

Compared to duloxetine non-exposed, the risk of minor malformation was increased in the unadjusted analyses with an OR of 1.42 (95% CI, 1.11-1.82). The OR attenuated in the adjusted and PS-matched analyses and became statistically non-significant: 1.15 (95% CI, 0.89-1.49) and 1.09 ((95% CI, 0.82-1.45), respectively.

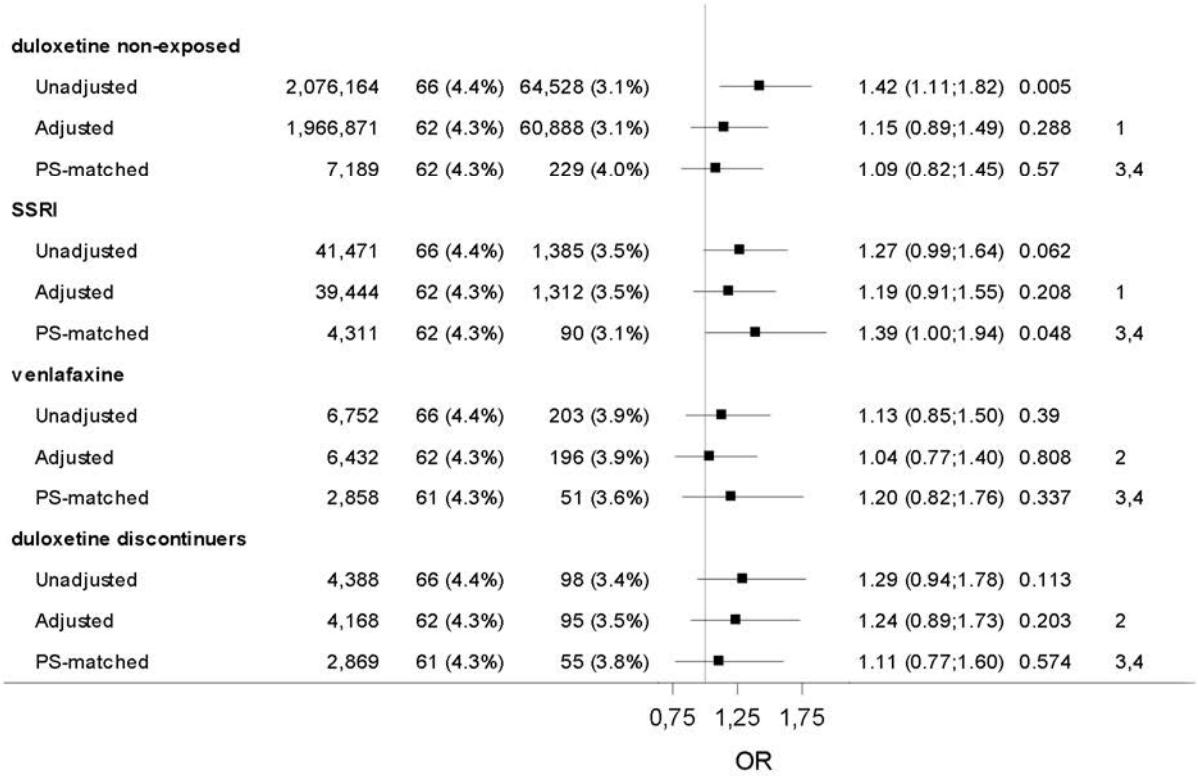
When comparing to SSRI, some point estimates indicated a higher risk for minor malformation, however, statistically non-significant or borderline significant: 1.27 (95% CI, 0.99-1.64), 1.19 (95% CI, 0.91-1.55), 1.39 (95% CI, 1.00-1.94) for unadjusted, adjusted and PS-matched analyses, respectively.

Compared to venlafaxine and duloxetine prior pregnancy, all results obtained were statistically non-significant: 1.13 (95% CI, 0.85-1.50), 1.04 (95% CI, 0.77-1.40) and 1.20 (95% CI, 0.82-1.76), (unadjusted, adjusted and PS-matched analyses) for women exposed to venlafaxine and 1.29 (95% CI, 0.94-1.78), 1.24 (95% CI, 0.89-1.73) and 1.11 (95% CI, 0.77-1.60), (unadjusted, adjusted and PS-matched analyses) for duloxetine discontinuers.

For minor malformation, the unadjusted analyses of duloxetine exposed compared to duloxetine non-exposed showed a statistically significant increased risk. However, this tendency was reduced, and became statistically non-significant in the adjusted and PS matched analyses. When compared to SSRI exposed, venlafaxine exposed and duloxetine discontinuers, some point estimates showed an increased risk for minor malformation for duloxetine exposed, however, they were found to be statistically non-significant or borderline significant suggesting no association.

Minor Malformation. Duloxetine vs four comparators

Comparator	Total N	duloxetine Events(%)	Comparator Events(%)	OR (95% CI)	P-value	Marker
duloxetine non-exposed						
Unadjusted	2,076,164	66 (4.4%)	64,528 (3.1%)	1.42 (1.11;1.82)	0.005	
Adjusted	1,966,871	62 (4.3%)	60,888 (3.1%)	1.15 (0.89;1.49)	0.288	1
PS-matched	7,189	62 (4.3%)	229 (4.0%)	1.09 (0.82;1.45)	0.57	3,4
SSRI						
Unadjusted	41,471	66 (4.4%)	1,385 (3.5%)	1.27 (0.99;1.64)	0.062	
Adjusted	39,444	62 (4.3%)	1,312 (3.5%)	1.19 (0.91;1.55)	0.208	1
PS-matched	4,311	62 (4.3%)	90 (3.1%)	1.39 (1.00;1.94)	0.048	3,4
venlafaxine						
Unadjusted	6,752	66 (4.4%)	203 (3.9%)	1.13 (0.85;1.50)	0.39	
Adjusted	6,432	62 (4.3%)	196 (3.9%)	1.04 (0.77;1.40)	0.808	2
PS-matched	2,858	61 (4.3%)	51 (3.6%)	1.20 (0.82;1.76)	0.337	3,4
duloxetine discontinuers						
Unadjusted	4,388	66 (4.4%)	98 (3.4%)	1.29 (0.94;1.78)	0.113	
Adjusted	4,168	62 (4.3%)	95 (3.5%)	1.24 (0.89;1.73)	0.203	2
PS-matched	2,869	61 (4.3%)	55 (3.8%)	1.11 (0.77;1.60)	0.574	3,4



Exposure definition: ≥1 redeemed prescription. N: Number of observations in analyses. OR: Odds ratio for Minor Malformation for duloxetine vs. comparators CI: Wald 95% confidence intervals

Marker 1: Adjusted for data source (Sweden/Denmark), age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, smoking, previous spontaneous abortion, previous stillbirths, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, renal failure, depression, affective, anxiety or phobia, severe stress reaction, diabetic peripheral neuropathic pain, glucose lowering, antihypertensive, fluconazole, estradiol, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination), progesterone (combination), antithyroid (combination).

Marker 2: Adjusted for data source (Sweden/Denmark), age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, smoking, previous spontaneous abortion, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, depression, affective, anxiety or

phobia, severe stress reaction, glucose lowering, antihypertensive, fluconazole, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination), progesterone (combination).
Marker 3: Conditional logistic regression.
Marker 4: Propensity score based on data source (Sweden/Denmark), age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, smoking, previous spontaneous abortion, previous stillbirths, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, renal failure, depression, affective, anxiety or phobia, severe stress reaction, diabetic peripheral neuropathic pain, glucose lowering, antihypertensive, fluconazole, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination).

Sensitivity analyses

Overall, similar patterns were observed in the sensitivity analyses to support what was observed in the main analyses. See Supplementary material, Section 2.2.

10.5.3. Abortion – spontaneous. Cox regression

The incidence rate of spontaneous abortion was 119.6 per 1,000 (95% CI, 101.4-137.9) in women exposed to duloxetine (145 events among 1,212 exposed women). For the comparator group of duloxetine non-exposed, the incidence rate was 104.4 per 1,000 (95% CI, 103.8-104.9) (corresponding to 106,309 events among 1,018,745 women).

For the other three comparator groups, the incidence rate of spontaneous abortion was 102.3 per 1,000 (95% CI 98.8-105.8) in women exposed to SSRI (2,900 events among 28,345 exposed women); 101.3 per 1,000 (95% CI 92.8-109.7) in women exposed to venlafaxine (497 events among 4,908 exposed women) and 118.5 per 1,000 (95% CI 101.7-135.3) in duloxetine discontinuers (168 events among 1,418 exposed women).

Compared to duloxetine non-exposed, the risk of spontaneous abortion was increased in the unadjusted analyses with an HR of 1.34 (95% CI, 1.14-1.58). The HR attenuated in the adjusted and PS-matched analyses and became statistically non-significant: 1.14 (95% CI, 0.96-1.34) and 1.08 ((95% CI, 0.89-1.31), respectively. A similar tendency was observed when comparing to venlafaxine: 1.23 (95% CI, 1.02-1.48), unadjusted; 1.18 (95% CI, 0.98-1.42), adjusted and 1.08 (95% CI, 0.82-1.41), PS-matched.

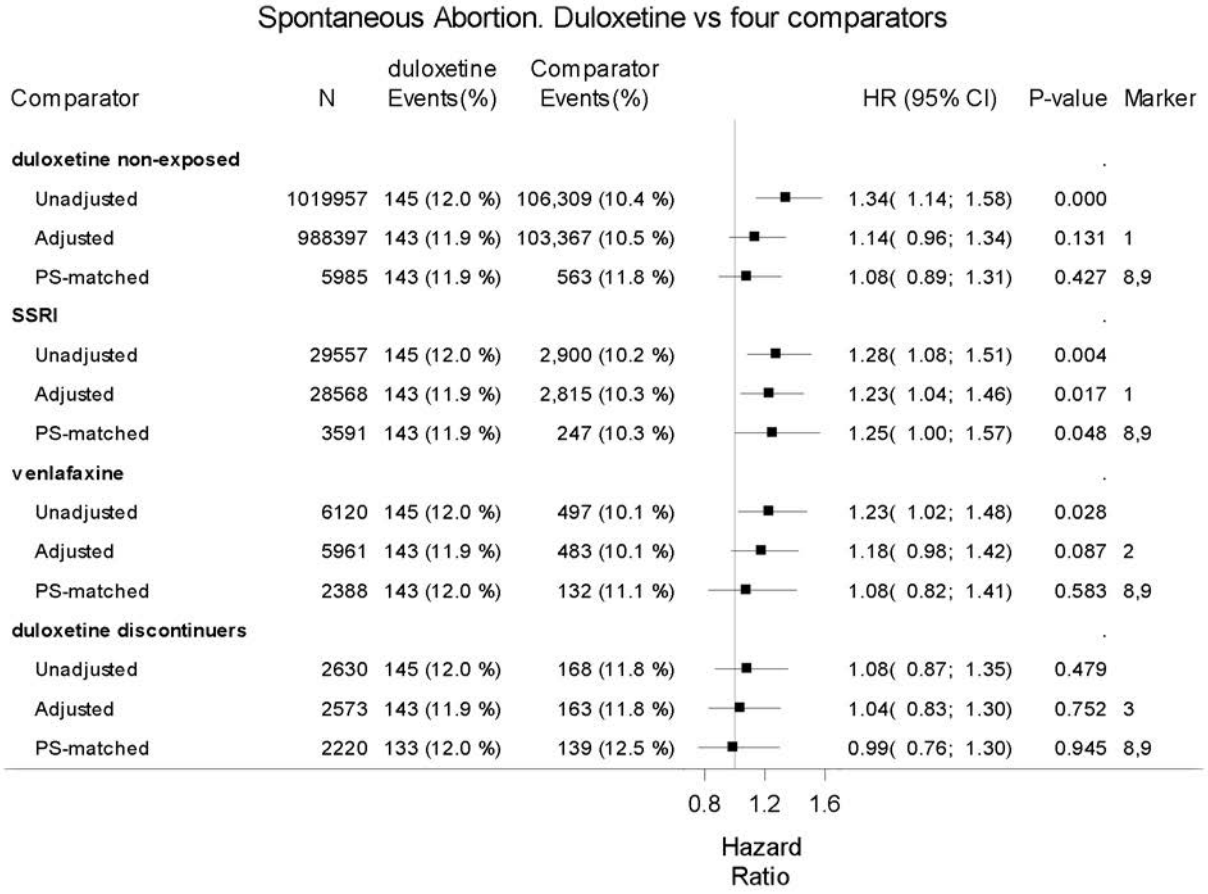
When compared to SSRI exposed, an increased risk of spontaneous abortion was observed with an HR of 1.28 (95% CI, 1.08-1.51) for the unadjusted analyses and 1.23 (95% CI, 1.02-1.48) for the adjusted analyses. For the PS-matched analyses, the HR was borderline statistically significant: 1.25 (95% CI, 1.00-1.57).

No increase in risk of spontaneous abortion was observed compared to duloxetine discontinuers: 1.08 (95% CI, 0.87-1.35); 1.04 (95% CI, 0.83- 1.30) and 0.99 (95% CI, 0.76-1.30) for the unadjusted, adjusted and PS-matched analyses, respectively.

In summary, for spontaneous abortion, the unadjusted analyses of duloxetine exposed compared to duloxetine non-exposed showed a statistically significant increased risk. However, this tendency was reduced and became statistically non-significant in the adjusted and PS matched analyses. A similar tendency was observed when compared to venlafaxine exposed.

When compared to SSRI exposed, a statistically significant increased risk of spontaneous abortion for duloxetine exposed was observed, for both adjusted and unadjusted analyses.

No statistically significant difference in risk was observed when duloxetine exposed and duloxetine discontinuers were compared.



Exposure definition: ≥1 redeemed prescription. N: Number of observations in analyses, HR: Hazard ratio for spontaneous abortion for duloxetine vs. comparators, CI: Wald 95% confidence intervals

Marker 1: Adjusted for age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, renal failure, depression, affective, anxiety or phobia, severe stress reaction, glucose lowering, antihypertensive, fluconazole, estradiol, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination), progesterone (combination), antithyroid (combination).

Marker 2: Adjusted for age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, depression, affective, anxiety or phobia, severe stress reaction, glucose lowering, antihypertensive, fluconazole,

estradiol, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination), progesterone (combination).

Marker 3: Adjusted for age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, renal failure, depression, affective, anxiety or phobia, severe stress reaction, glucose lowering, antihypertensive, fluconazole, estradiol, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination), progesterone (combination).

Marker 8: Conditional logistic regression.

Marker 9: Propensity score based on age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, renal failure, depression, affective, anxiety or phobia, severe stress reaction, glucose lowering, antihypertensive, fluconazole, estradiol, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination), progesterone (combination), antithyroid (combination).

Sensitivity analyses

Figures for sensitivity analyses are found in the supplementary material, Section 2.3. However, the results for the main and sensitivity analyses for spontaneous abortion are heterogenous and are therefore summarized in Table 10.9 (statistically significant estimates are marked in bold):

Table 10.9 Overview of estimates for spontaneous abortions (Cox regression).

Exposure/cohort definintion	Model	Duloxetine unexposed	SSRIs exposed	Venlafaxine exposed	Duloxetine discontinuers
≥1 redeemed prescription					
	Unadjusted	**1.34 (1.14; 1.58)**	**1.28 (1.08; 1.51)**	**1.23 (1.02; 1.48)**	1.08 (0.87; 1.35)
	Adjusted	1.14 (0.96; 1.34)	**1.23 (1.04; 1.46)**	1.18 (0.98; 1.42)	1.04 (0.83; 1.30)
	PS-matched	1.08 (0.89; 1.31)	**1.25 (1.00; 1.57)**	1.08 (0.82; 1.41)	0.99 (0.76; 1.30)
≥2 redeemed prescriptions					
	Unadjusted	**1.32 (1.06; 1.64)**	**1.96 (1.56; 2.45)**	**1.60 (1.24; 2.06)**	1.04 (0.80; 1.36)
	Adjusted	1.14 (0.91; 1.41)	**2.00 (1.58; 2.52)**	**1.58 (1.22; 2.05)**	1.05 (0.80; 1.38)
	PS-matched	1.12 (0.87; 1.45)	**1.97 (1.44; 2.71)**	1.37 (0.94; 2.00)	1.03 (0.73; 1.47)
Overlap of redeemed prescription and exposure time window					
	Unadjusted	**1.34 (1.14; 1.56)**	**1.22 (1.04; 1.43)**	1.16 (0.97; 1.38)	1.05 (0.85; 1.30)
	Adjusted	1.13 (0.97; 1.32)	1.15 (0.98; 1.36)	1.13 (0.94; 1.35)	1.01 (0.81; 1.27)
	PS-matched	1.11 (0.92; 1.33)	1.06 (0.86; 1.31)	1.07 (0.83; 1.37)	0.98 (0.76; 1.28)
First observed pregnancy					
	Unadjusted	**1.62 (1.30; 2.01)**	**1.46 (1.17; 1.83)**	**1.45 (1.13; 1.87)**	1.34 (0.98; 1.83)
	Adjusted	**1.32 (1.05; 1.64)**	**1.44 (1.14; 1.81)**	**1.46 (1.13; 1.90)**	1.34 (0.96; 1.86)
	PS-matched	**1.34 (1.03; 1.74)**	1.25 (0.93; 1.69)	1.23 (0.84; 1.81)	1.22 (0.82; 1.80)

Estimates are shown as Hazard Ratios (HR) with 95% confidence intervals. Statistically significant estimates are highlighted in bold.

In the sensitivity analyses of women with more than one redeemed prescription an increased risk was observed for duloxetine exposed compared to SSRI and venlafaxine exposed. The risk was doubled compared to SSRI exposed. In the sensitivity analyses including only the first observed pregnancy the results showed an increased risk for all comparators, although some of the odds ratios were not statistically significant. On the other hand, in the sensitivity defining exposure as overlap between days' supply and exposure window, no increased risk across comparator groups was found.

10.5.4. Abortion – spontaneous. Logistic regression

This is a post hoc analyses where the analyses of spontaneous abortion are performed in the same population, but using a logistic regression, instead of a Cox regression model.

Overall, the post hoc analyses showed similar findings compared to the ad hoc analyses, using Cox regression models.

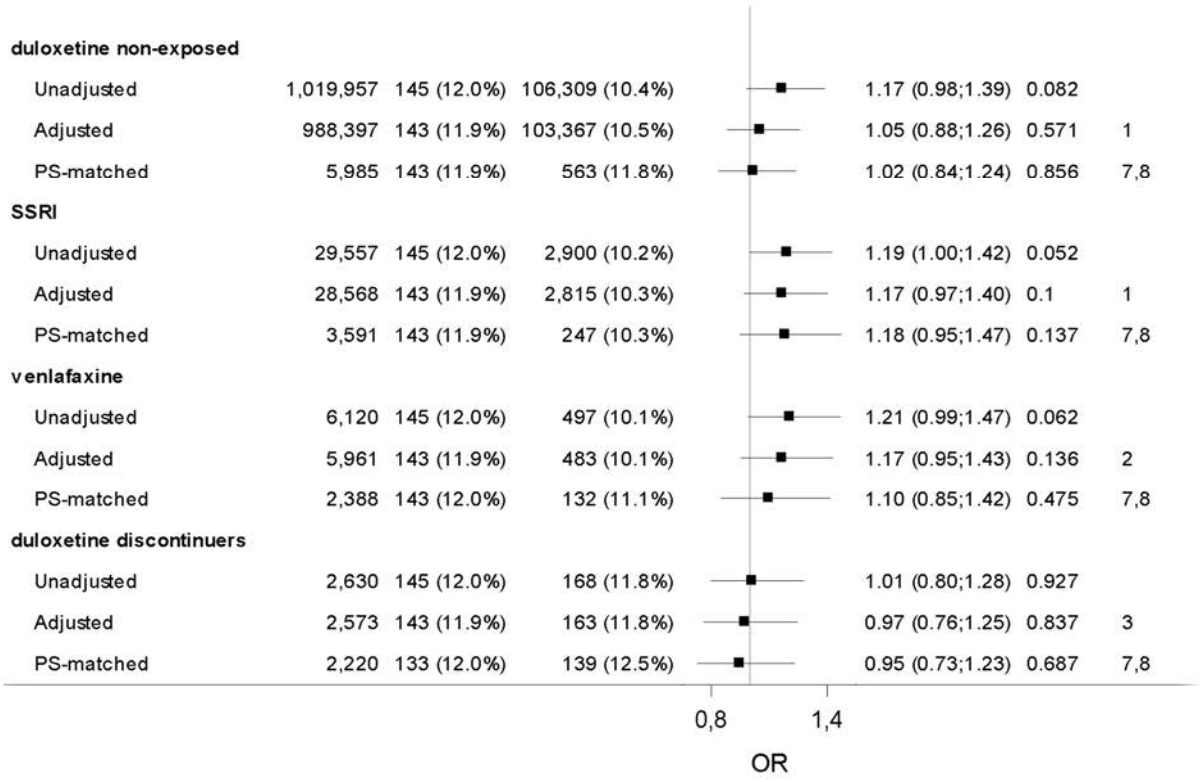
Compared to duloxetine non-exposed, OR point estimate of the unadjusted analysis indicated a slightly higher risk for spontaneous abortion, however, statistically non-significant. 1.17 (95% CI, 0.98-1.39). The OR point estimate attenuated in the adjusted and PS-matched analyses: 1.05 (95% CI, 0.88-1.26) and 1.02 (95% CI, 0.84-1.24).

When compared to SSRI exposed, a slightly higher risk of spontaneous abortion was observed for the unadjusted analysis, with an OR borderline statistically significant: 1.19 (95% CI, 1.00-1.42), and non-significant for the adjusted and PS-matched analyses: 1.17 (95% CI, 0.97-1.40) and 1.18 (95% CI, 0.95-1.47). The same pattern was observed compared to venlafaxine, however, statistically non-significant for all three analyses: 1.21 (95% CI, 0.99-1.47); 1.17 (95% CI, 0.95- 1.43) and 1.10 (95% CI, 0.85-1.42) for the unadjusted, adjusted and PS-matched analyses, respectively.

No increase in risk of spontaneous abortion was observed compared to duloxetine discontinuers: 1.01 (95% CI, 0.80-1.28); 0.97 (95% CI, 0.76- 1.25) and 0.95 (95% CI, 0.73-1.23) for the unadjusted, adjusted and PS-matched analyses, respectively.

Spontaneous Abortion. Duloxetine vs four comparators - Logistic regression

Comparator	Total N	duloxetine Events(%)	Comparator Events(%)	OR (95% CI)	P-value	Marker
duloxetine non-exposed						
Unadjusted	1,019,957	145 (12.0%)	106,309 (10.4%)	1.17 (0.98;1.39)	0.082	
Adjusted	988,397	143 (11.9%)	103,367 (10.5%)	1.05 (0.88;1.26)	0.571	1
PS-matched	5,985	143 (11.9%)	563 (11.8%)	1.02 (0.84;1.24)	0.856	7,8
SSRI						
Unadjusted	29,557	145 (12.0%)	2,900 (10.2%)	1.19 (1.00;1.42)	0.052	
Adjusted	28,568	143 (11.9%)	2,815 (10.3%)	1.17 (0.97;1.40)	0.1	1
PS-matched	3,591	143 (11.9%)	247 (10.3%)	1.18 (0.95;1.47)	0.137	7,8
venlafaxine						
Unadjusted	6,120	145 (12.0%)	497 (10.1%)	1.21 (0.99;1.47)	0.062	
Adjusted	5,961	143 (11.9%)	483 (10.1%)	1.17 (0.95;1.43)	0.136	2
PS-matched	2,388	143 (12.0%)	132 (11.1%)	1.10 (0.85;1.42)	0.475	7,8
duloxetine discontinuers						
Unadjusted	2,630	145 (12.0%)	168 (11.8%)	1.01 (0.80;1.28)	0.927	
Adjusted	2,573	143 (11.9%)	163 (11.8%)	0.97 (0.76;1.25)	0.837	3
PS-matched	2,220	133 (12.0%)	139 (12.5%)	0.95 (0.73;1.23)	0.687	7,8



Exposure definition: ≥1 redeemed prescription. N: Number of observations in analyses.

OR: Odds ratio for spontaneous abortion for duloxetine vs. comparators

CI: Wald 95% confidence intervals

Marker 1: Adjusted for age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, renal failure, depression, affective, anxiety or phobia, severe stress reaction, glucose lowering, antihypertensive, fluconazole, estradiol, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination), progesterone (combination), antithyroid (combination).

Marker 2: Adjusted for age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, depression, affective, anxiety or phobia, severe stress reaction, antihypertensive, fluconazole, estradiol, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination), progesterone (combination).

Marker 3: Adjusted for age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, depression, affective, anxiety or phobia, severe stress reaction, antihypertensive, fluconazole, estradiol, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination), progesterone (combination).

Marker 7: Conditional logistic regression.

Marker 8: Propensity score based on age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, renal failure, depression, affective, anxiety or phobia, severe stress reaction, glucose lowering, antihypertensive, fluconazole, estradiol, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination), progesterone (combination), antithyroid (combination).

Sensitivity analyses

As for the Cox model, results for the main and sensitivity analyses for spontaneous abortion were heterogenous and were therefore summarized in the following Table 10.10 (statistically significant estimates are marked in bold):

Table 10.10 Overview of estimates for spontaneous abortions (logistic regression).

Exposure/cohort definintion	Model	Duloxetine unexposed	SSRIs exposed	Venlafaxine exposed	Duloxetine discontinuers
≥1 redeemed prescription					
	Unadjusted	1.17 (0.98;1.39)	**1.19 (1.00;1.42)**	1.21 (0.99;1.47)	1.01 (0.80;1.28)
	Adjusted	1.05 (0.88;1.26)	1.17 (0.97;1.40)	1.17 (0.95;1.43)	0.97 (0.76;1.25)
	PS-matched	1.02 (0.84;1.24)	1.18 (0.95;1.47)	1.10 (0.85;1.42)	0.95 (0.73;1.23)
≥2 redeemed prescriptions					
	Unadjusted	1.17 (0.93;1.47)	**1.74 (1.37;2.21)**	**1.54 (1.17;2.01)**	1.02 (0.77;1.35)
	Adjusted	1.06 (0.84;1.35)	**1.77 (1.38;2.28)**	**1.48 (1.12;1.96)**	1.02 (0.76;1.38)
	PS-matched	1.03 (0.79;1.33)	**1.50 (1.11;2.02)**	**1.51 (1.06;2.15)**	1.07 (0.77;1.49)
Overlap between redeemed prescription and exposure time window					
	Unadjusted	1.16 (0.98;1.37)	1.15 (0.97;1.36)	1.14 (0.95;1.38)	0.97 (0.77;1.22)
	Adjusted	1.05 (0.88;1.24)	1.10 (0.93;1.31)	1.12 (0.93;1.36)	0.94 (0.74;1.20)
	PS-matched	1.07 (0.89;1.29)	0.99 (0.80;1.22)	1.05 (0.83;1.33)	0.94 (0.73;1.21)
First observed pregnancy					
	Unadjusted	**1.45 (1.15;1.84)**	**1.41 (1.11;1.80)**	**1.45 (1.11;1.90)**	1.30 (0.93;1.82)
	Adjusted	**1.28 (1.00;1.63)**	**1.38 (1.07;1.77)**	**1.46 (1.10;1.94)**	1.34 (0.94;1.91)
	PS-matched	**1.34 (1.02;1.76)**	1.31 (0.97;1.76)	**1.47 (1.01;2.13)**	1.42 (0.97;2.08)

Estimates are shown as Odds Ratios (OR) with 95% confidence intervals. Statistically significant estimates are highlighted in bold.

The results of the sensitivity analyses are comparable to the results when using a Cox model (Table 10.9). An increased risk compared to SSRI and venlafaxine exposed for women redeeming more than one prescription during pregnancy was observed. The risk was approximately 50% increased. In the cohort including only the first observed pregnancy, the results showed an increased risk for all comparators, although some of the ORs were not

statistically significant. On the other hand, defining exposure as days' supply, no increased risk across comparator groups was found.

10.5.5. Abortion – elective. Cox regression

The incident rate of elective abortion was 335.0 per 1,000 (95% CI, 308.4-361.6) in women exposed to duloxetine (406 events among 1,212 exposed women). For the comparator group of duloxetine non-exposed, the incidence rate was 150.9 per 1,000 (95% CI, 150.2-151.6) (corresponding to 153,691 events among 1,018,745 women).

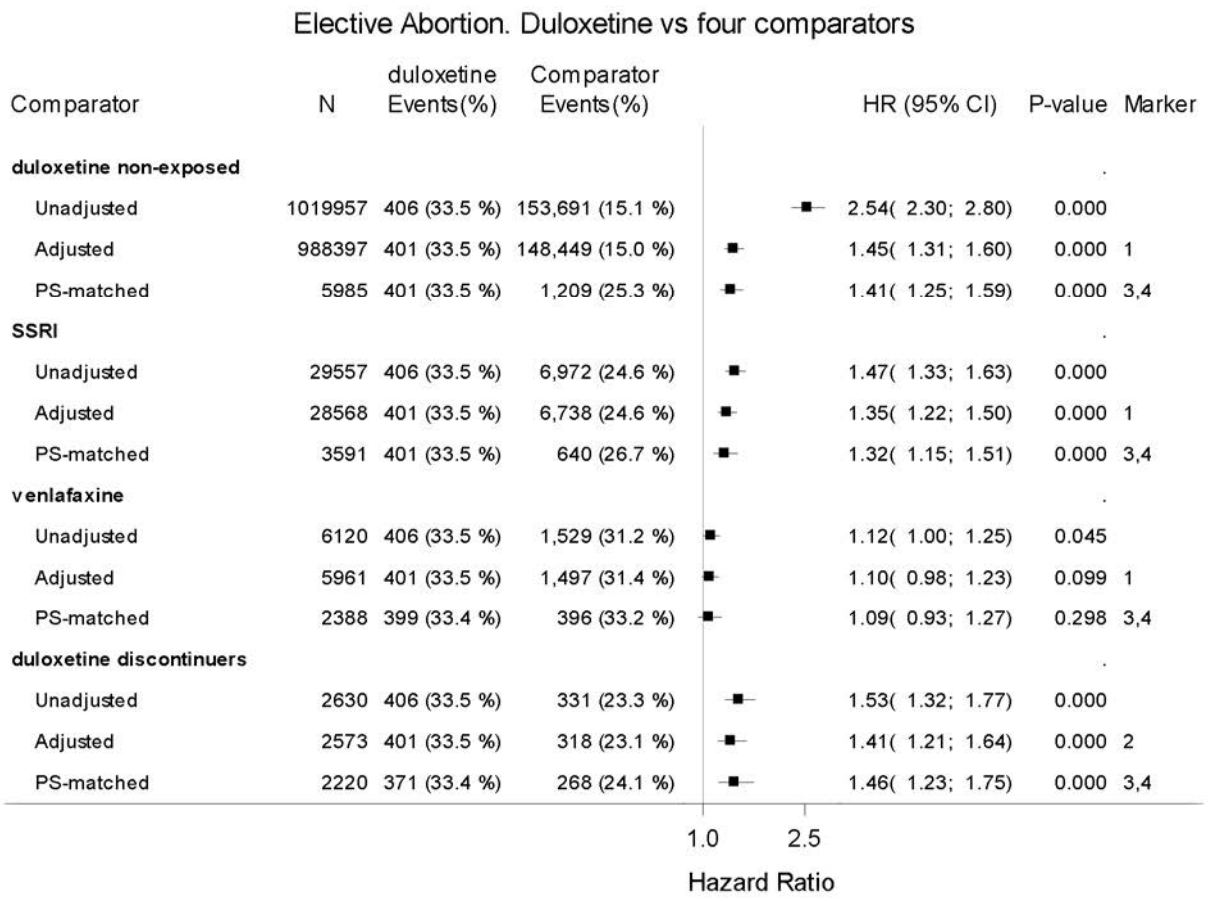
For the other three comparator groups, the incidence rate of elective abortion was 246.0 per 1,000 (95% CI 241.0-251.0) in women exposed to SSRI (6,972 events among 28,345 exposed women); 311.5 per 1,000 (95% CI 298.6-324.5) in women exposed to venlafaxine (1,529 events among 4,908 exposed women) and 233.4 per 1,000 (95% CI 211.4-255.4) in duloxetine discontinuers (331 events among 1,418 exposed women).

Compared to duloxetine non-exposed, the risk of elective abortion was increased with a HR of 2.54 (95% CI, 2.30-2.80). The HR is reduced in the adjusted and PS-matched analyses: 1.45 (95% CI, 1.31-1.60) and 1.41 (95% CI, 1.25-1.59), respectively.

The same pattern was observed when compared to SSRI exposed and women exposed to duloxetine prior pregnancy.
SSRI: 1.47 (95% CI, 1.33-1.63), unadjusted; 1.35 (95% CI, 1.22-1.50), adjusted and 1.32 (95% CI, 1.15-1.51), PS-matched. Duloxetine prior pregnancy: 1.53 (95% CI, 1.32-1.77) unadjusted; 1.41 (95% CI, 1.21-1.64), adjusted and 1.46 (95% CI, 1.23-1.75), PS-matched.

No increase in risk of elective abortion was observed compared to venlafaxine exposed: 1.12 (95% CI, 1.00-1.25); 1.10 (95% CI, 0.98- 1.23) and 1.09 (95% CI, 0.93-1.27) for the unadjusted, adjusted and PS-matched analyses, respectively.

In conclusion, when compared to duloxetine non-exposed, SSRI exposed and duloxetine discontinuers, a strong, highly statistically significant increased risk for elective abortion was observed for duloxetine exposed. When compared to venlafaxine exposed no difference was found.



Exposure definition: ≥1 redeemed prescription. N: Number of observations in analyses, HR: Hazard ratio for Elective abortion for duloxetine vs. comparators, CI: Wald 95% confidence intervals

Marker 1: Adjusted for age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, renal failure, depression, affective, anxiety or phobia, severe stress reaction, glucose lowering, antihypertensive, fluconazole, estradiol, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination), progesterone (combination), antithyroid (combination).

Marker 2: Adjusted for age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, renal failure, depression, affective, anxiety or phobia, severe stress reaction, glucose lowering, antihypertensive, fluconazole, estradiol, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination), progesterone (combination).

Marker 3: Cox regression stratified on propensity score matching-group.

Marker 4: Propensity score based on age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, renal failure, depression, affective, anxiety or phobia, severe stress reaction, glucose lowering, antihypertensive, fluconazole, estradiol, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination), progesterone (combination), antithyroid (combination).

Sensitivity analyses

In the sensitivity analyses similar patterns were observed. See Supplementary material, Section 2.5.

10.5.6. Stillbirths

In general, analyses of stillbirth were limited due to lack of statistical power. Because of very few events, adjusted analyses could not be conducted, and only some of the sensitivity analyses could be conducted: The sensitivity analyses where drug exposure was redefined to overlap between redeemed prescription and exposure time window (days' supply), and the sensitivity analyses including BMI as a covariate.

The incidence rate of stillbirths was 3.0 per 1,000 (95% CI, 0.4-5.6) in women exposed to duloxetine (5 events among 1,668 exposed women). For the comparator group of duloxetine non-exposed, the incidence rate was 3.6 per 1,000 (95% CI, 3.5-3.7) (corresponding to 7,694 events among 2,130,773 women).

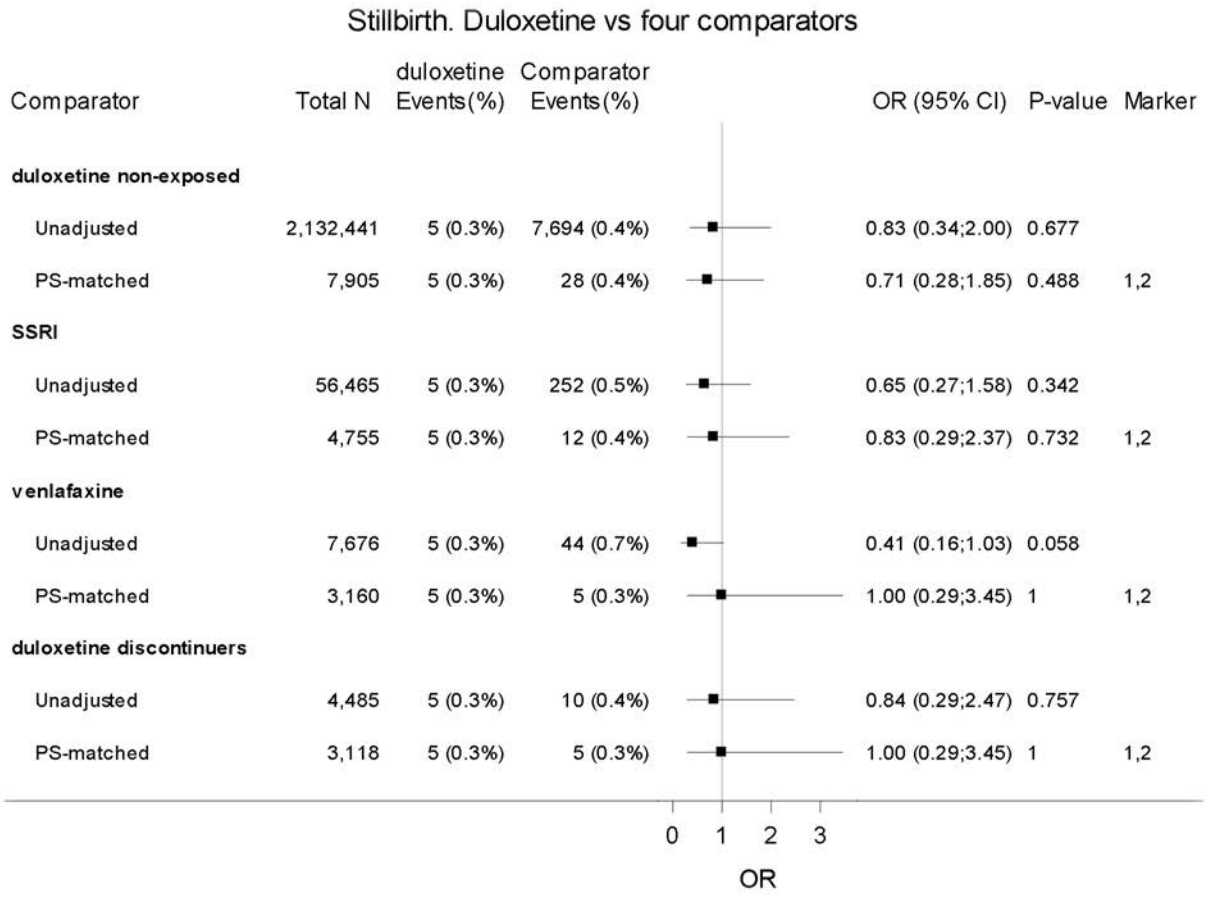
For the other three comparator groups, the incidence rate of stillbirth was 4.6 per 1,000 (95% CI 4.0-5.2) in women exposed to SSRI (252 events among 54,797 exposed women); 7.3 per 1,000 (95% CI 5.2-9.5) in women exposed to venlafaxine (44 events among 6,008 exposed women) and 3.5 per 1,000 (95% CI 1.4-5.7) in duloxetine discontinuers (10 events among 2,817 exposed women).

Compared to duloxetine non-exposed, the estimated OR was 0.83 (95% CI, 0.34-2.00) and 0.71 (95% CI, 0.28-1.85) for the unadjusted and PS-matched analyses, respectively.

The same pattern was observed when compared to SSRI exposed, venlafaxine exposed and exposed to duloxetine prior pregnancy, where the OR from the PS-matched analyses was: 0.83 (95% CI, 0.29-2.37), 1.00 (95% CI, 0.29-3.45) and 1.00 (95% CI, 0.29-3.45), respectively.

It has to be noted that all results have wide confidence intervals and were statistically non-significant.

In conclusion, all analyses suggested no increased risk of stillbirths for duloxetine exposed across all comparison groups.



Exposure definition: ≥1 redeemed prescription. N: Number of observations in analyses.

OR: Odds ratio for Stillbirth for duloxetine vs. comparators

CI: Wald 95% confidence intervals

Marker 1: Conditional logistic regression.

Marker 2: Propensity score based on data source (Sweden/Denmark), age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, smoking, previous spontaneous abortion, previous stillbirths, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, renal failure, depression, affective, anxiety or phobia, severe stress reaction, diabetic peripheral neuropathic pain, glucose lowering, antihypertensive, fluconazole, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination), antithyroid (combination).

Sensitivity analyses

A similar pattern was observed in the sensitivity analyses to support what was observed in the main analyses. See Supplementary material, Section 2.6.

10.5.7. Small for gestational age – without malformation. Early exposure time window

The incidence rate of SGA, without malformation was 96.3 per 1,000 (95% CI, 81.5-111.2) in women exposed to duloxetine (146 events among 1,516 exposed women). For the comparator group of duloxetine non-exposed, the incidence rate was 94.2 per 1,000 (95% CI, 93.8-94.6) (corresponding to 188,122 events among 1,996,843 women).

For the other three comparator groups, the incidence rate of SGA, without malformation was 101.2 per 1,000 (95% CI 98.4-104.0) in women exposed to SSRI (4,509 events among 44,569 exposed women); 93.4 per 1,000 (95% CI 85.6-101.2) in women exposed to venlafaxine (502 events among 5,375 exposed women) and 90.7 per 1,000 (95% CI 79.8-101.5) in duloxetine discontinuers (244 events among 2,691 exposed women).

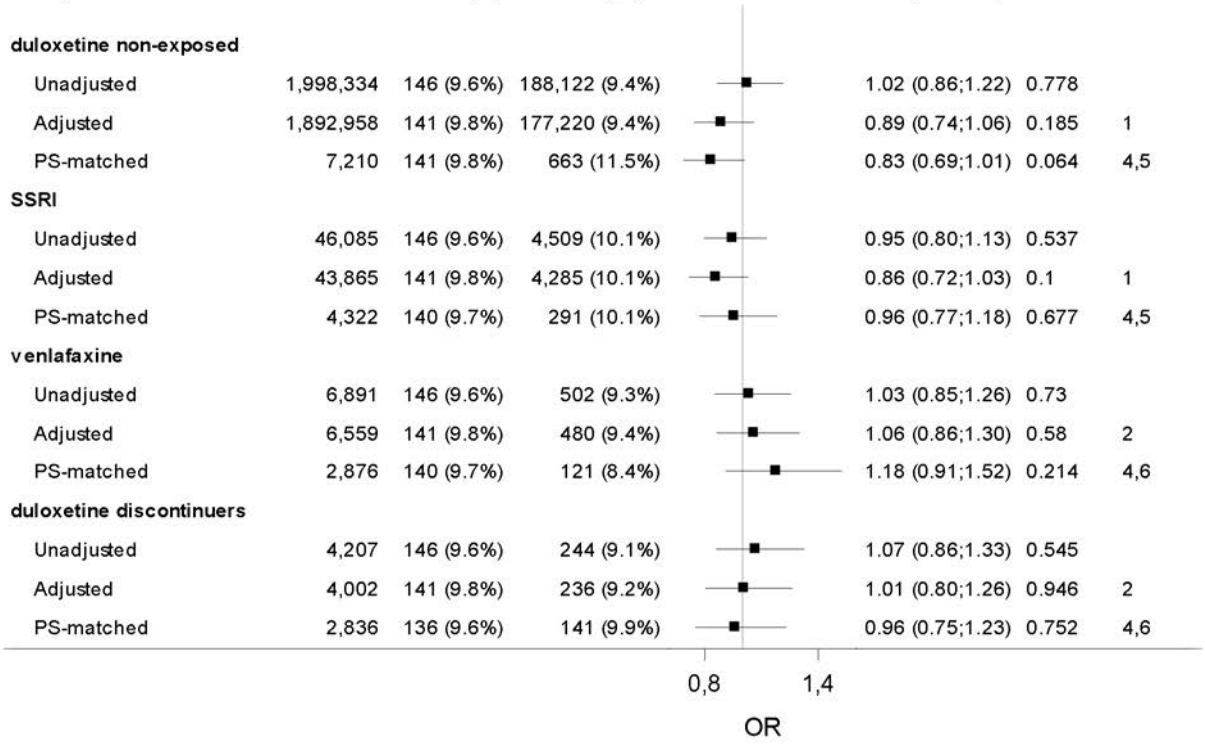
No increased risk of SGA, without malformation was observed comparing to duloxetine non-exposed. The estimated ORs were 1.02 (95% CI, 0.86-1.22); 0.89 (95% CI, 0.74-1.06) and 0.83 (95% CI, 0.69-1.01) for the unadjusted, unadjusted and PS-matched analyses, respectively.

A similar pattern was observed when compared to SSRI exposed and exposed to duloxetine prior pregnancy, where the OR from the PS-matched analyses was: 0.96 (95% CI, 0.77-1.18) and 0.96 (95% CI, 0.75-1.23), respectively. Compared to venlafaxine a slightly increased risk was observed in the PS-match analysis, however, statistically non-significant: 1.18 (95% CI, 0.91-1.52).

To conclude overall, all analyses suggested no increased risk of SGA, without malformation for duloxetine exposed across all comparison groups, when exposed in the early exposure time period.

Small for Gestational Age (SGA), Early exposure period, without malformations. Duloxetine vs four comparators

Comparator	Total N	duloxetine Events(%)	Comparator Events(%)	OR (95% CI)	P-value	Marker
duloxetine non-exposed						
Unadjusted	1,998,334	146 (9.6%)	188,122 (9.4%)	1.02 (0.86;1.22)	0.778	
Adjusted	1,892,958	141 (9.8%)	177,220 (9.4%)	0.89 (0.74;1.06)	0.185	1
PS-matched	7,210	141 (9.8%)	663 (11.5%)	0.83 (0.69;1.01)	0.064	4,5
SSRI						
Unadjusted	46,085	146 (9.6%)	4,509 (10.1%)	0.95 (0.80;1.13)	0.537	
Adjusted	43,865	141 (9.8%)	4,285 (10.1%)	0.86 (0.72;1.03)	0.1	1
PS-matched	4,322	140 (9.7%)	291 (10.1%)	0.96 (0.77;1.18)	0.677	4,5
venlafaxine						
Unadjusted	6,891	146 (9.6%)	502 (9.3%)	1.03 (0.85;1.26)	0.73	
Adjusted	6,559	141 (9.8%)	480 (9.4%)	1.06 (0.86;1.30)	0.58	2
PS-matched	2,876	140 (9.7%)	121 (8.4%)	1.18 (0.91;1.52)	0.214	4,6
duloxetine discontinuers						
Unadjusted	4,207	146 (9.6%)	244 (9.1%)	1.07 (0.86;1.33)	0.545	
Adjusted	4,002	141 (9.8%)	236 (9.2%)	1.01 (0.80;1.26)	0.946	2
PS-matched	2,836	136 (9.6%)	141 (9.9%)	0.96 (0.75;1.23)	0.752	4,6



Exposure definition: ≥1 redeemed prescription. N: Number of observations in analyses.

OR: Odds ratio for SGA for duloxetine vs. comparators

CI: Wald 95% confidence intervals

Marker 1: Adjusted for data source (Sweden/Denmark), age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, smoking, previous spontaneous abortion, previous stillbirths, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, renal failure, depression, affective, anxiety or phobia, severe stress reaction, glucose lowering, antihypertensive, fluconazole, estradiol, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination), progesterone (combination), antithyroid (combination).

Marker 2: Adjusted for data source (Sweden/Denmark), age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, smoking, previous spontaneous abortion, previous stillbirths, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, renal failure, depression, affective, anxiety or phobia, severe stress reaction, glucose lowering, antihypertensive, fluconazole, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination), progesterone (combination).

Marker 3: Adjusted for data source (Sweden/Denmark), age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, smoking, previous spontaneous abortion, previous stillbirths, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, depression,

affective, anxiety or phobia, severe stress reaction, glucose lowering, antihypertensive, fluconazole, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination), progesterone (combination).
Marker 4: Conditional logistic regression.
Marker 5: Propensity score based on data source (Sweden/Denmark), age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, smoking, previous spontaneous abortion, previous stillbirths, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, renal failure, depression, affective, anxiety or phobia, severe stress reaction, , diabetic peripheral neuropathic pain, glucose lowering, antihypertensive, fluconazole, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination), antithyroid (combination).
Marker 6: Propensity score based on data source (Sweden/Denmark), age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, smoking, previous spontaneous abortion, previous stillbirths, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, renal failure, depression, affective, anxiety or phobia, severe stress reaction, , diabetic peripheral neuropathic pain, glucose lowering, antihypertensive, fluconazole, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination).

Sensitivity analyses

Similar pattern was observed in the sensitivity analyses, showing no increased risk of SGA. See Supplementary material, Section 2.7.

10.5.8. Small for gestational age – without malformation. Late exposure time window

The incidence rate of SGA, without malformation was 82.0 per 1,000 (95% CI, 55.9-108.0) in women exposed to duloxetine (35 events among 427 exposed women). For the comparator group of duloxetine non-exposed, the incidence rate was 94.2 per 1,000 (95% CI, 93.8-94.6) (corresponding to 188,233 events among 1,997,932 women).

For the other three comparator groups, the incidence rate of SGA, without malformation was 101.4 per 1,000 (95% CI 98.2-104.5) in women exposed to SSRI (3,631 events among 35,821 exposed women); 85.1 per 1,000 (95% CI 75.3-95.0) in women exposed to venlafaxine (262 events among 3,078 exposed women) and 93.6 per 1,000 (95% CI 84.0-103.1) in duloxetine discontinuers (335 events among 3,580 exposed women).

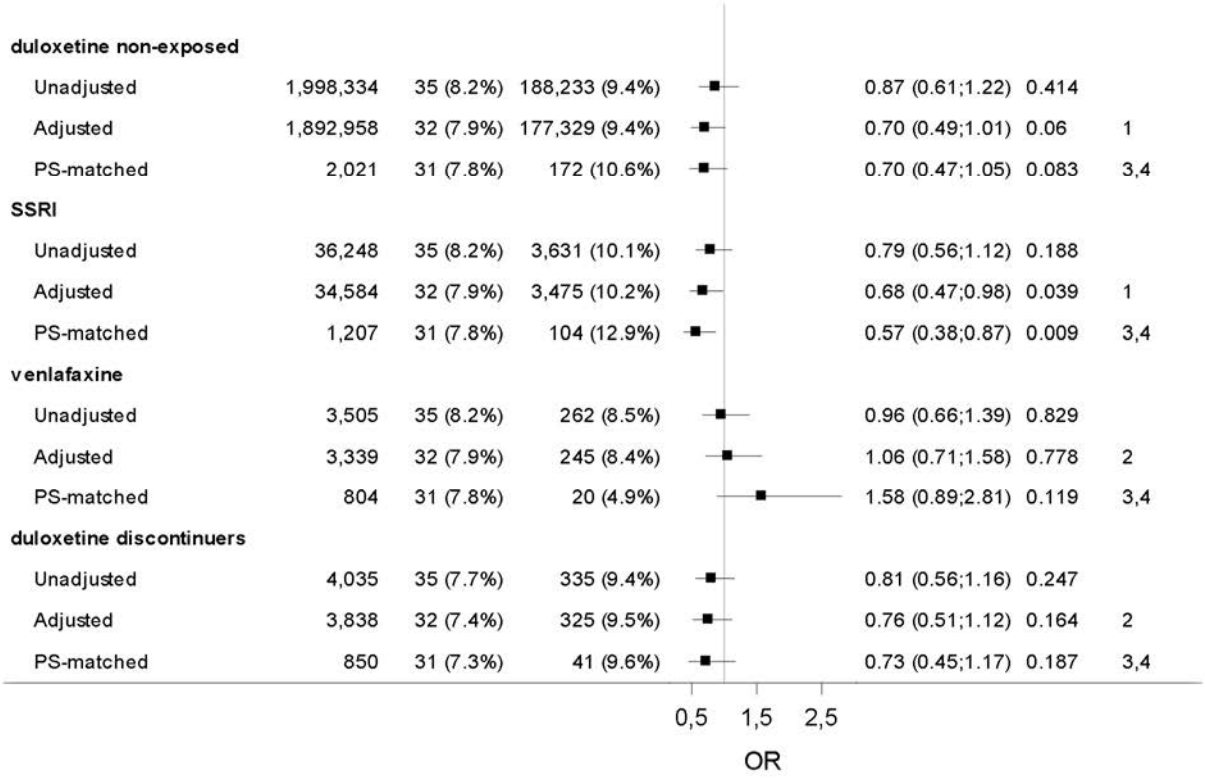
No increased risk of SGA, without malformation was observed comparing to duloxetine non-exposed. The estimated ORs were 0.87 (95% CI, 0.61-1.22); 0.70 (95% CI, 0.49-1.01) and 0.70 (95% CI, 0.47-1.05) for the unadjusted, unadjusted and PS-matched analyses, respectively.

A similar pattern was observed when compared to venlafaxine exposed and exposed to duloxetine discontinuers, where the OR from the PS-matched analyses was: 1.58 (95% CI, 0.89-2.81) and 0.73 (95% CI, 0.45-1.17), respectively. Compared to SSRI a lower risk was observed in the PS-match analysis, statistically significant: 0.57 (95% CI, 0.38-0.87).

In conclusion, point estimates for SGA suggested no increased risk for duloxetine exposed compared to duloxetine non-exposed, SSRI exposed and duloxetine exposed prior to pregnancy, when exposed in the late exposure time period.

Small for Gestational Age (SGA), Late exposure period, without malformations

Comparator	Total N	duloxetine Events(%)	Comparator Events(%)	OR (95% CI)	P-value	Marker
duloxetine non-exposed						
Unadjusted	1,998,334	35 (8.2%)	188,233 (9.4%)	0.87 (0.61;1.22)	0.414	
Adjusted	1,892,958	32 (7.9%)	177,329 (9.4%)	0.70 (0.49;1.01)	0.06	1
PS-matched	2,021	31 (7.8%)	172 (10.6%)	0.70 (0.47;1.05)	0.083	3,4
SSRI						
Unadjusted	36,248	35 (8.2%)	3,631 (10.1%)	0.79 (0.56;1.12)	0.188	
Adjusted	34,584	32 (7.9%)	3,475 (10.2%)	0.68 (0.47;0.98)	0.039	1
PS-matched	1,207	31 (7.8%)	104 (12.9%)	0.57 (0.38;0.87)	0.009	3,4
venlafaxine						
Unadjusted	3,505	35 (8.2%)	262 (8.5%)	0.96 (0.66;1.39)	0.829	
Adjusted	3,339	32 (7.9%)	245 (8.4%)	1.06 (0.71;1.58)	0.778	2
PS-matched	804	31 (7.8%)	20 (4.9%)	1.58 (0.89;2.81)	0.119	3,4
duloxetine discontinuers						
Unadjusted	4,035	35 (7.7%)	335 (9.4%)	0.81 (0.56;1.16)	0.247	
Adjusted	3,838	32 (7.4%)	325 (9.5%)	0.76 (0.51;1.12)	0.164	2
PS-matched	850	31 (7.3%)	41 (9.6%)	0.73 (0.45;1.17)	0.187	3,4



Exposure definition: ≥1 redeemed prescription. N: Number of observations in analyses.

OR: Odds ratio for SGA for duloxetine vs. comparators

CI: Wald 95% confidence intervals

Marker 1: Adjusted for data source (Sweden/Denmark), age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, smoking, previous spontaneous abortion, previous stillbirths, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, renal failure, depression, affective, anxiety or phobia, severe stress reaction, glucose lowering, antihypertensive, fluconazole, estradiol, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination), progesterone (combination), antithyroid (combination).

Marker 2: Adjusted for data source (Sweden/Denmark), age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, smoking, previous spontaneous abortion, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, depression, affective, anxiety or

phobia, severe stress reaction, glucose lowering, antihypertensive, fluconazole, thyroid, NSAID, opioids, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination).

Marker 3: Conditional logistic regression.

Marker 4: Propensity score based on data source (Sweden/Denmark), age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, smoking, previous spontaneous abortion, previous stillbirths, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, renal failure, depression, affective, anxiety or phobia, severe stress reaction, glucose lowering, antihypertensive, fluconazole, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination).

Sensitivity analyses

The same pattern was observed for the sensitivity analyses, showing no increased risk for duloxetine exposed across comparator groups. See Supplementary material, Section 2.8.

10.5.9. Small for gestational age – with malformation. Early exposure time window

In general, analyses of SGA among births with malformations were limited due to lack of statistical power. Because of very few events, adjusted analyses could not be conducted, and only some of the sensitivity analyses could be conducted: The sensitivity analyses where drug exposure was redefined to overlap between redeemed prescription and exposure time window (days' supply), and the sensitivity analyses including BMI as a covariate.

The incidence rate of SGA, with malformation was 150.7 per 1,000 (95% CI, 68.6-232.7) in women exposed to duloxetine (11 events among 73 exposed women). For the comparator group of duloxetine non-exposed, the incidence rate was 131.8 per 1,000 (95% CI, 129.5-134.0) (corresponding to 11,043 events among 83,817 women).

For the other three comparator groups, the incidence rate of SGA, with malformation was 127.6 per 1,000 (95% CI 113.5-141.7) in women exposed to SSRI (275 events among 2,155 exposed women); 123.6 per 1,000 (95% CI 84.1-163.1) in women exposed to venlafaxine (33 events among 267 exposed women) and 87.8 per 1,000 (95% CI 42.2-133.4) in duloxetine discontinuers (13 events among 148 exposed women).

No increased risk of SGA, with malformation was observed comparing to duloxetine non-exposed. The estimated ORs were 1.17 (95% CI, 0.62-2.22) and 1.16 (95% CI, 0.55-2.46) for the unadjusted and PS-matched analyses, respectively.

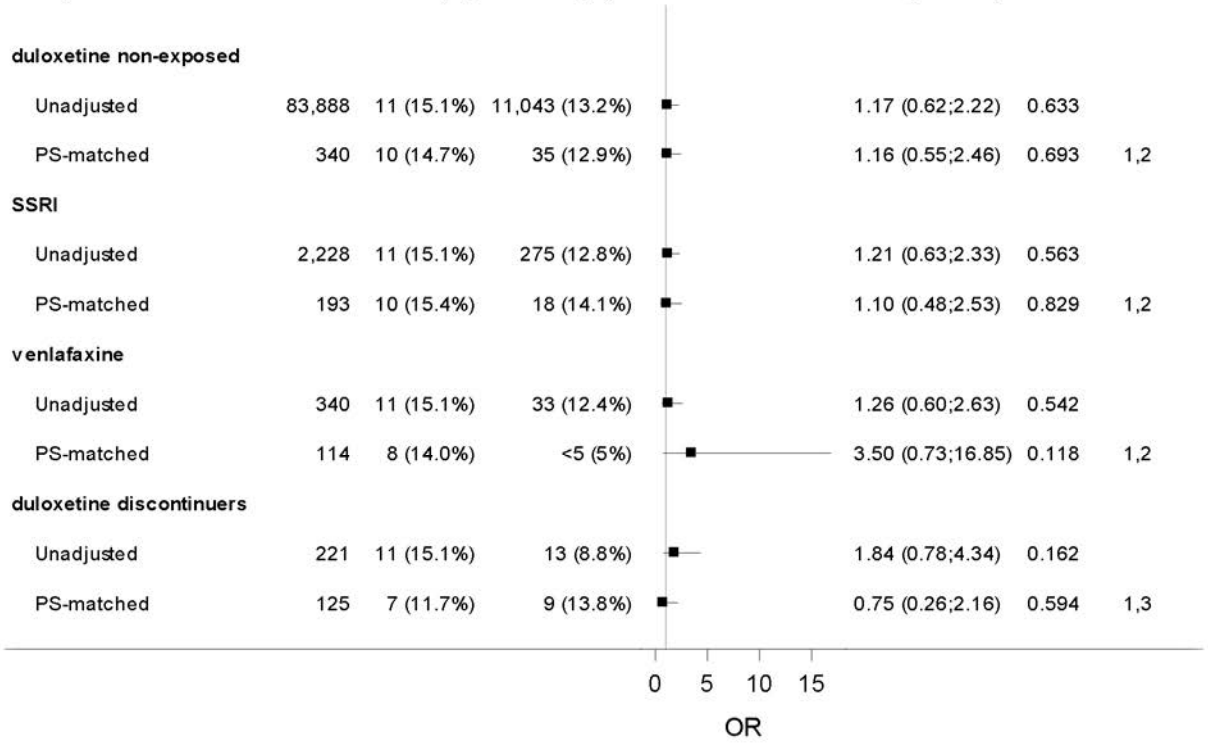
A similar pattern was observed when compared to SSRI exposed and exposed to duloxetine prior to pregnancy, where ORs from the PS-matched analyses were: 1.10 (95% CI, 0.48-2.53) and 0.75 (95% CI, 0.26-2.16), respectively. An exception was the point estimate obtained comparing to venlafaxine, suggesting a highly increased risk of SGA, among births with malformation, however, statistically non-significant and with very wide confidence intervals: 3.50 (95% CI, 0.73-16.85).

In general, it should be noted that all results were statistically non-significant and with wide confidence intervals.

In conclusion of the primary analyses, the OR point estimates were close to 1 and confidence intervals were wide in the analyses using PS matching, suggesting no association across comparison groups. One exception was a point estimate suggesting a highly increased risk of giving birth to a child SGA, among the births with malformation, for duloxetine exposed when compared with venlafaxine, however, statistically non-significant and with very wide confidence intervals.

Small for Gestational Age (SGA), Early exposure period, with malformations. Duloxetine vs four comparators

Comparator	Total N	duloxetine Events(%)	Comparator Events(%)	OR (95% CI)	P-value	Marker
duloxetine non-exposed						
Unadjusted	83,888	11 (15.1%)	11,043 (13.2%)	1.17 (0.62;2.22)	0.633	
PS-matched	340	10 (14.7%)	35 (12.9%)	1.16 (0.55;2.46)	0.693	1,2
SSRI						
Unadjusted	2,228	11 (15.1%)	275 (12.8%)	1.21 (0.63;2.33)	0.563	
PS-matched	193	10 (15.4%)	18 (14.1%)	1.10 (0.48;2.53)	0.829	1,2
venlafaxine						
Unadjusted	340	11 (15.1%)	33 (12.4%)	1.26 (0.60;2.63)	0.542	
PS-matched	114	8 (14.0%)	<5 (5%)	3.50 (0.73;16.85)	0.118	1,2
duloxetine discontinuers						
Unadjusted	221	11 (15.1%)	13 (8.8%)	1.84 (0.78;4.34)	0.162	
PS-matched	125	7 (11.7%)	9 (13.8%)	0.75 (0.26;2.16)	0.594	1,3



Exposure definition: ≥1 redeemed prescription. N: Number of observations in analyses.

OR: Odds ratio for SGA for duloxetine vs. comparators

CI: Wald 95% confidence intervals

Women who have a redeemed duloxetine prescription 3 months before but not during pregnancy are removed.

Analyses are conditioned on children with malformations.

Marker 1: Conditional logistic regression.

Marker 2: Propensity score based on data source (Sweden/Denmark), age (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, smoking, previous spontaneous abortion, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, obesity, depression, affective, anxiety or phobia, severe stress reaction, fluconazole, thyroid, opioids, triptans, antiepileptics, corticosteroid (combination)

Marker 3: Propensity scores based on data source (Sweden/Denmark), household income, year (grouped), psychiatric hospital, psychiatric outpatient, smoking, previous spontaneous abortion, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, obesity, depression, affective, anxiety or phobia, severe stress reaction, fluconazole, thyroid, opioids, triptans, antiepileptics, corticosteroid (combination)

Sensitivity analyses

Similar patterns were seen in the sensitivity analyses. See Supplementary material, Section 2.9.

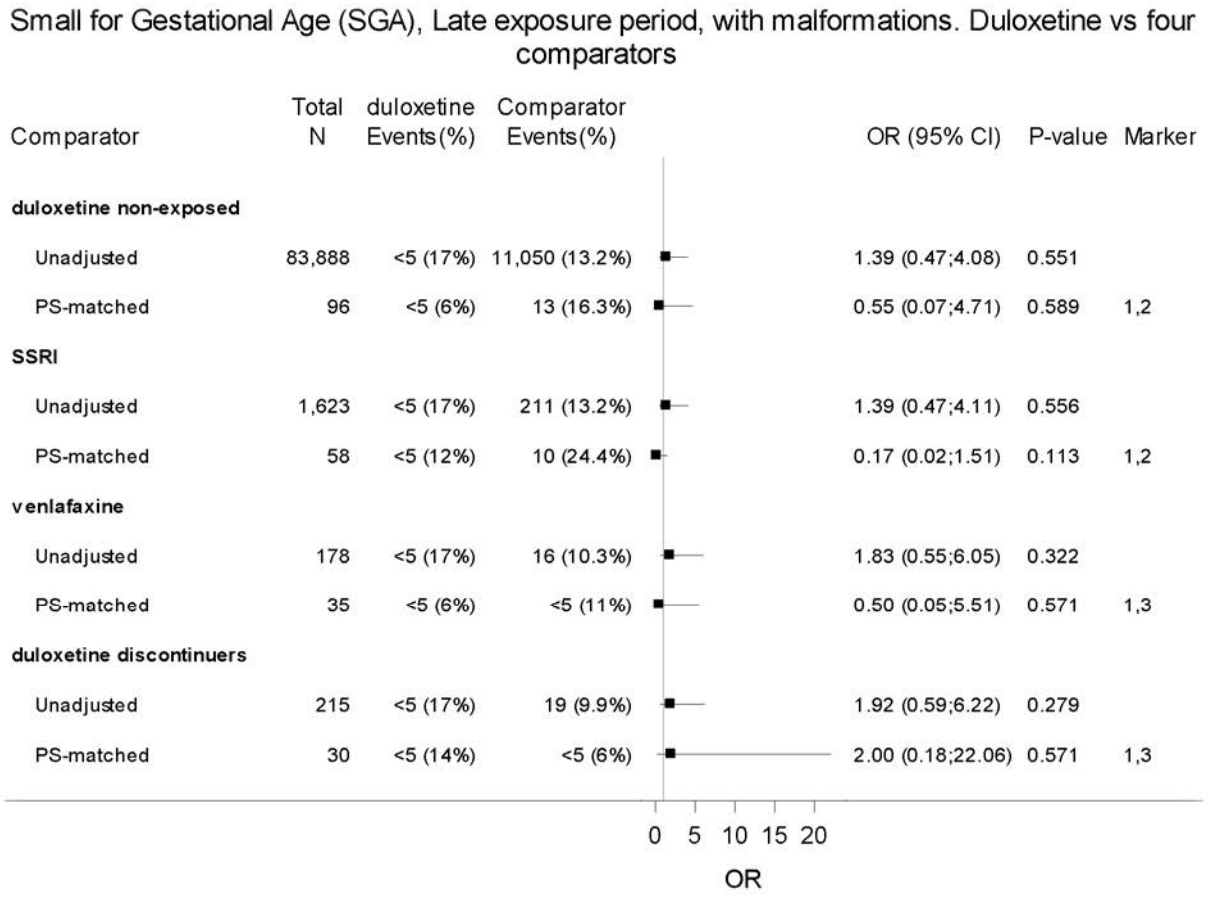
10.5.10. Small for gestational age – with malformation. Late exposure time window

In general, analyses of SGA among birth with malformation were limited due to lack of statistical power. Because of very few events, adjusted analyses could not be conducted, and only some of the sensitivity analyses could be conducted: The sensitivity analyses where drug exposure was redefined to overlap between redeemed prescription and exposure time window, and the sensitivity analyses including BMI as covariate.

There were less than 5 events of giving birth to a child SGA, with malformation among duloxetine exposed which does not allow for the incidence rate to be published. For the comparator group of duloxetine non-exposed, the incidence rate was 131.8 per 1,000 (95% CI, 129.5-134) (corresponding to 11,050 events among 83,867 women).

For the other three comparator groups, the incidence rate of small for gestational age, with malformation was 131.9 per 1,000 (95% CI 115.3-148.5) in women exposed to SSRI (211 events among 1,600 exposed women); 103.2 per 1,000 (95% CI 55.3-151.1) in women exposed to venlafaxine (16 events among 155 exposed women) and 99.0 per 1,000 (95% CI 56.7-141.2) in duloxetine discontinuers (19 events among 192 exposed women).

All point estimates obtained are statistically non-significant, with very wide confidence interval, and do not allow for clear interpretations.



Exposure definition: ≥1 redeemed prescription. N: Number of observations in analyses.

OR: Odds ratio for SGA for duloxetine vs. comparators

CI: Wald 95% confidence intervals

Women who have a redeemed duloxetine prescription 3 months before but not during pregnancy are removed.

Analyses are conditioned on children with malformations.

Marker 1: Conditional logistic regression.

Marker 2: Propensity scores are based on: data source (Sweden/Denmark), household income, year (grouped), psychiatric outpatient, smoking, previous spontaneous abortion, hyper or hypothyroidism, obesity, depression, affective, anxiety or phobia, severe stress reaction, thyroid, opioids, antipsychotics, anxiolytics, corticosteroid (combination)

Marker 3: Propensity scores are based on: data source (Sweden/Denmark), household income, year (grouped), psychiatric outpatient, smoking, previous spontaneous abortion, hyper or hypothyroidism, obesity, depression, affective, severe stress reaction, thyroid, opioids, antipsychotics, anxiolytics, corticosteroid (combination)

Sensitivity analyses

Similar patterns were seen in the sensitivity analyses. See Supplementary material, Section 2.10.

10.5.11. Small for gestational age – no stratification on major malformation. Early exposure time window

This is a post hoc analysis where the analyses of preterm birth are repeated, but without stratification on presence and absence of malformation. Below are the analyses of preterm birth with the early exposure time window.

The incidence rate of SGA, no stratification on major malformation was 98.8 per 1,000 (95% CI, 84.1-113.5) in women exposed to duloxetine. For the comparator group of duloxetine non-exposed, the incidence rate was 95.7 per 1,000 (95% CI, 95.3-96.1; 199,165 events among 2,080,660 women).

For the other three comparator groups, the incidence rate of SGA, no stratification on major malformation was 102.4 per 1,000 (95% CI 99.6-105.1) in women exposed to SSRI (4,784 events among 46,724 exposed women); 94.8 per 1,000 (95% CI 87.2-102.5) in women exposed to venlafaxine (535 events among 5,642 exposed women) and 90.5 per 1,000 (95% CI 80.0-101.1) in duloxetine discontinuers (257 events among 2,839 exposed women).

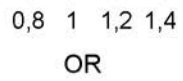
No increased risk of SGA, no stratification on major malformation was observed comparing to duloxetine non-exposed. The estimated ORs were 1.04 (95% CI, 0.88-1.22); 0.90 (95% CI, 0.76-1.07) and 0.88 (95% CI, 0.73-1.08) for the unadjusted, adjusted and PS-matched analyses, respectively.

A similar pattern was observed when compared to SSRI exposed, venlafaxine exposed and exposed to duloxetine prior pregnancy, where ORs from the PS-matched analyses were: 0.84 (95% CI, 0.69-1.04); 1.03 (95% CI, 0.81-1.30) and 1.05 (95% CI, 0.83-1.34), respectively.

In conclusion, in this post hoc analyses of SGA (without malformation stratification), the primary analyses showed no association for duloxetine exposed across comparison groups for the early exposure time period.

Small for Gestational Age (SGA), Early exposure period. Duloxetine vs four comparators

Comparator	Total N	duloxetine Events(%)	Comparator Events(%)	OR (95% CI)	P-value	Marker
duloxetine non-exposed						
Unadjusted	2,082,442	157 (9.9%)	199,188 (9.6%)	1.04 (0.88;1.22)	0.672	
Adjusted	1,971,834	151 (10.0%)	187,496 (9.5%)	0.90 (0.76;1.07)	0.224	1
PS-matched	7,550	151 (10.0%)	678 (11.2%)	0.88 (0.73;1.06)	0.17	14,4
SSRI						
Unadjusted	48,315	157 (9.9%)	4,784 (10.2%)	0.96 (0.81;1.14)	0.648	
Adjusted	45,947	151 (10.0%)	4,537 (10.2%)	0.87 (0.73;1.04)	0.127	2
PS-matched	4,539	151 (10.0%)	350 (11.6%)	0.84 (0.69;1.04)	0.105	14,4
venlafaxine						
Unadjusted	7,231	157 (9.9%)	535 (9.5%)	1.05 (0.87;1.26)	0.634	
Adjusted	6,882	151 (10.0%)	511 (9.5%)	1.07 (0.88;1.31)	0.498	2
PS-matched	3,004	150 (10.0%)	146 (9.7%)	1.03 (0.81;1.30)	0.809	14,5
duloxetine discontinuers						
Unadjusted	4,428	157 (9.9%)	257 (9.1%)	1.10 (0.89;1.36)	0.364	
Adjusted	4,208	151 (10.0%)	249 (9.2%)	1.04 (0.84;1.30)	0.704	2
PS-matched	3,008	149 (9.9%)	142 (9.4%)	1.05 (0.83;1.34)	0.667	14,5



Exposure definition: ≥1 redeemed prescription. N: Number of observations in analyses.

OR: Odds ratio for SGA for duloxetine vs. comparators

CI: Wald 95% confidence intervals

Marker 1: Adjusted for data source (Sweden/Denmark), age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, smoking, previous spontaneous abortion, previous stillbirths, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, renal failure, depression, affective, anxiety or phobia, severe stress reaction, diabetic peripheral neuropathic pain, glucose lowering, antihypertensive, fluconazole, estradiol, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination), progesterone (combination), antithyroid (combination).

Marker 2: Adjusted for data source (Sweden/Denmark), age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, smoking, previous spontaneous abortion, previous stillbirths, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, renal failure, depression, affective, anxiety or phobia, severe stress reaction, glucose lowering, antihypertensive, fluconazole, estradiol, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination), progesterone (combination), antithyroid (combination).

Marker 4: Propensity score based on data source (Sweden/Denmark), age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, smoking, previous spontaneous abortion, previous stillbirths, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, renal failure, depression, affective, anxiety or phobia, severe stress reaction, diabetic peripheral neuropathic pain, glucose

lowering, antihypertensive, fluconazole, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination), antithyroid (combination).
Marker 5: Propensity score based on data source (Sweden/Denmark), age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, smoking, previous spontaneous abortion, previous stillbirths, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, renal failure, depression, affective, anxiety or phobia, severe stress reaction, diabetic peripheral neuropathic pain, glucose lowering, antihypertensive, fluconazole, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination),.
Marker 14: Conditional logistic regression.

Sensitivity analyses

Similar patterns were observed in the sensitivity analyses. See Supplementary material, Section 2.11.

10.5.12. Small for gestational age – no stratification on major malformation. Late exposure time window

This is a post hoc analyses where analyses of preterm birth are repeated, but without stratification on presence or absence of malformation. Below are the analyses of preterm birth with the late exposure time window.

The incidence rate of SGA, no stratification on major malformation, was 86.7 per 1,000 (95% CI, 60.7-112.7) in women exposed to duloxetine. For the comparator group of duloxetine non-exposed, the incidence rate was 95.7 per 1,000 (95% CI, 95.3-96.1; 199283 events among 2,081,799 women).

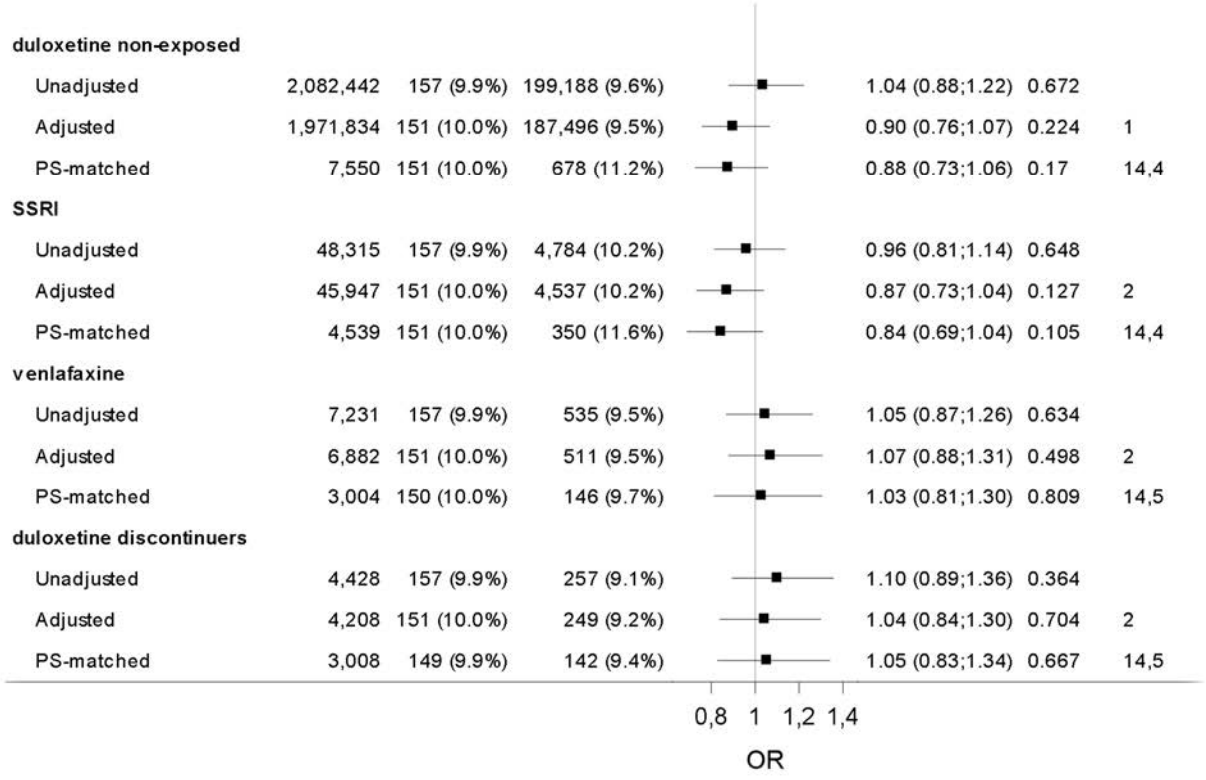
For the other three comparator groups, the incidence rate of SGA, no stratification on major malformation, was 102.7 per 1,000 (95% CI 99.6-105.7) in women exposed to SSRI (3,842 events among 37421 exposed women); 86.0 per 1,000 (95% CI 76.3-95.6) in women exposed to venlafaxine (278 events among 3,233 exposed women) and 93.8 per 1,000 (95% CI 84.5-103.2) in duloxetine discontinuers (354 events among 3772 exposed women).

No increased risk of SGA, no stratification on major malformation, was observed comparing to duloxetine non-exposed. The estimated ORs were 0.90 (95% CI, 0.65-1.25); 0.75 (95% CI, 0.53-1.06) and 0.64 (95% CI, 0.44-0.95) for the unadjusted, adjusted and PS-matched analyses, respectively. An exception was the point estimate obtained comparing to venlafaxine, suggesting an increased risk of SGA, however, the observation was statistically non-significant and with wide confidence intervals: 1.48 (95% CI, 0.85-2.57).

In this post hoc analysis of SGA (without malformation stratification), the primary analyses showed no association for duloxetine exposed across comparison groups for the late exposure time period.

Small for Gestational Age (SGA), Early exposure period. Duloxetine vs four comparators

Comparator	Total N	duloxetine Events(%)	Comparator Events(%)	OR (95% CI)	P-value	Marker
duloxetine non-exposed						
Unadjusted	2,082,442	157 (9.9%)	199,188 (9.6%)	1.04 (0.88;1.22)	0.672	
Adjusted	1,971,834	151 (10.0%)	187,496 (9.5%)	0.90 (0.76;1.07)	0.224	1
PS-matched	7,550	151 (10.0%)	678 (11.2%)	0.88 (0.73;1.06)	0.17	14,4
SSRI						
Unadjusted	48,315	157 (9.9%)	4,784 (10.2%)	0.96 (0.81;1.14)	0.648	
Adjusted	45,947	151 (10.0%)	4,537 (10.2%)	0.87 (0.73;1.04)	0.127	2
PS-matched	4,539	151 (10.0%)	350 (11.6%)	0.84 (0.69;1.04)	0.105	14,4
venlafaxine						
Unadjusted	7,231	157 (9.9%)	535 (9.5%)	1.05 (0.87;1.26)	0.634	
Adjusted	6,882	151 (10.0%)	511 (9.5%)	1.07 (0.88;1.31)	0.498	2
PS-matched	3,004	150 (10.0%)	146 (9.7%)	1.03 (0.81;1.30)	0.809	14,5
duloxetine discontinuers						
Unadjusted	4,428	157 (9.9%)	257 (9.1%)	1.10 (0.89;1.36)	0.364	
Adjusted	4,208	151 (10.0%)	249 (9.2%)	1.04 (0.84;1.30)	0.704	2
PS-matched	3,008	149 (9.9%)	142 (9.4%)	1.05 (0.83;1.34)	0.667	14,5



Exposure definition: ≥1 redeemed prescription. N: Number of observations in analyses.

OR: Odds ratio for SGA for duloxetine vs. comparators

CI: Wald 95% confidence intervals

Marker 1: Adjusted for data source (Sweden/Denmark), age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, smoking, previous spontaneous abortion, previous stillbirths, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, renal failure, depression, affective, anxiety or phobia, severe stress reaction, diabetic peripheral neuropathic pain, glucose lowering, antihypertensive, fluconazole, estradiol, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination), progesterone (combination), antithyroid (combination).

Marker 2: Adjusted for data source (Sweden/Denmark), age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, smoking, previous spontaneous abortion, previous stillbirths, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, renal failure, depression, affective, anxiety or phobia, severe stress reaction, glucose lowering, antihypertensive, fluconazole, estradiol, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination), progesterone (combination), antithyroid (combination).

Marker 3: Adjusted for data source (Sweden/Denmark), age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, smoking, previous spontaneous abortion, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, depression, affective, anxiety or phobia, severe stress reaction, glucose lowering, antihypertensive, fluconazole, estradiol, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination), progesterone (combination), antithyroid (combination).
Marker 4: Conditional logistic regression.
Marker 5: Propensity score based on data source (Sweden/Denmark), age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, smoking, previous spontaneous abortion, previous stillbirths, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, renal failure, depression, affective, anxiety or phobia, severe stress reaction, glucose lowering, antihypertensive, fluconazole, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination).
Marker 6: Adjusted for data source (Sweden/Denmark), age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, smoking, previous spontaneous abortion, previous stillbirths, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, renal failure, depression, affective, anxiety or phobia, severe stress reaction, glucose lowering, antihypertensive, fluconazole, estradiol, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination), progesterone (combination).

Sensitivity analyses

Similar patterns were observed in the sensitivity analyses. See Supplementary material, Section 2.12.

10.5.13. Preterm birth. Early exposure time window

The incidence rate of preterm birth was 115.2 per 1,000 (95% CI, 99.5-130.9) in women exposed to duloxetine (183 events among 1,589 exposed women). For the comparator group of duloxetine non-exposed, the incidence rate was 61.1 per 1,000 (95% CI, 60.8-61.4) (corresponding to 127,206 events among 2,080,880 women).

For the other three comparator groups, the incidence rate of preterm birth was 90.4 per 1,000 (95% CI, 87.8-93) in women exposed to SSRI (4,226 events among 46,726 exposed women); 127.1 per 1,000 (95% CI, 118.4-135.8) in women exposed to venlafaxine (717 events among 5,642 exposed women) and 95.8 per 1,000 (95% CI, 85-106.6) in duloxetine discontinuers (272 events among 2,839 exposed women);

Compared to duloxetine non-exposed unadjusted, adjusted and PS-matched analyses OR were 2.00 (95% CI, 1.72-2.33), 1.38 (95% CI, 1.17-1.63) and 1.33 (95% CI, 1.10-1.60), respectively.

Comparing to the other three comparators SSRI, venlafaxine and duloxetine discontinuers, OR were 1.21 (95% CI, 0.99-1.47); 0.91 (95% CI, 0.73-1.14) and 1.17 (95% CI, 0.93-1.49) for the PS-matched analyses.

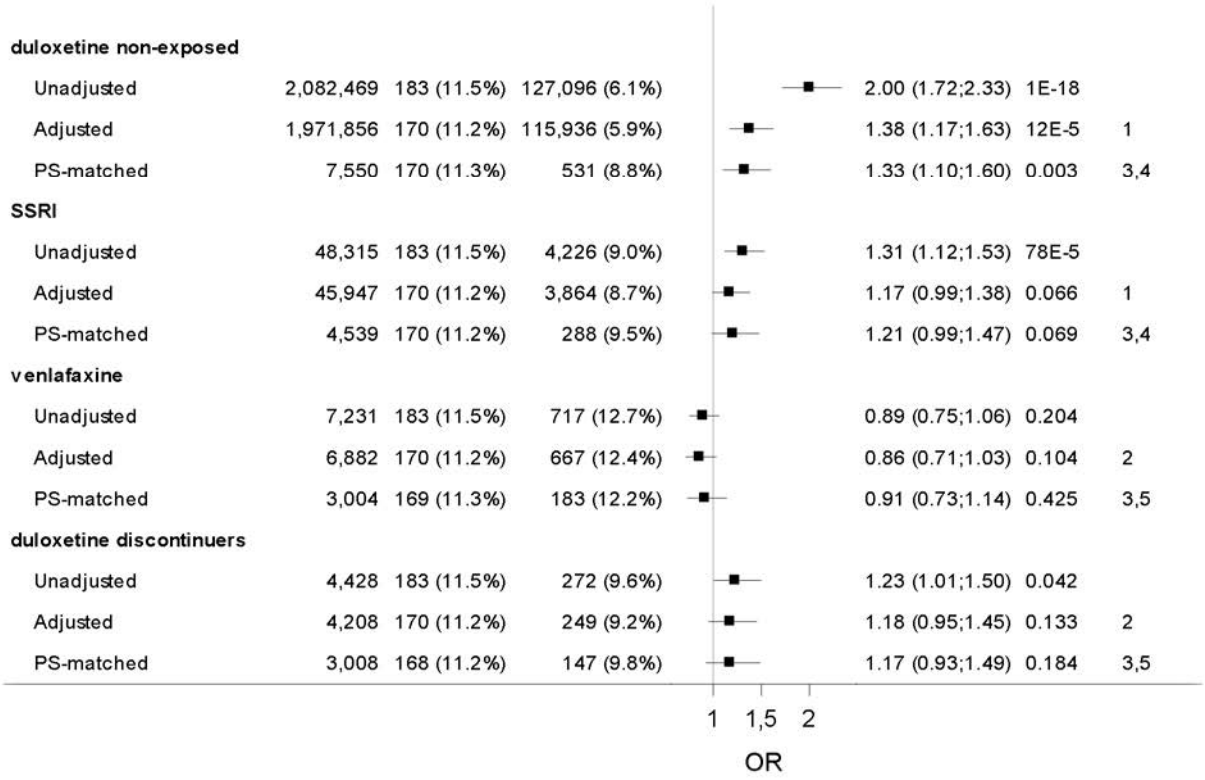
An increased risk of preterm birth was observed for duloxetine exposed when compared to duloxetine non-exposed, found to be statistically significant, when exposed in the early exposure time period.

A similar tendency was seen when duloxetine exposed were compared to SSRI exposed and duloxetine discontinuers, however, these associations were borderline non-significant.

No association was found when duloxetine exposed were compared to venlafaxine exposed.

Preterm birth, Early exposure period. Duloxetine vs four comparators

Comparator	Total N	duloxetine Events(%)	Comparator Events(%)	OR (95% CI)	P-value	Marker
duloxetine non-exposed						
Unadjusted	2,082,469	183 (11.5%)	127,096 (6.1%)	2.00 (1.72;2.33)	1E-18	
Adjusted	1,971,856	170 (11.2%)	115,936 (5.9%)	1.38 (1.17;1.63)	12E-5	1
PS-matched	7,550	170 (11.3%)	531 (8.8%)	1.33 (1.10;1.60)	0.003	3,4
SSRI						
Unadjusted	48,315	183 (11.5%)	4,226 (9.0%)	1.31 (1.12;1.53)	78E-5	
Adjusted	45,947	170 (11.2%)	3,864 (8.7%)	1.17 (0.99;1.38)	0.066	1
PS-matched	4,539	170 (11.2%)	288 (9.5%)	1.21 (0.99;1.47)	0.069	3,4
venlafaxine						
Unadjusted	7,231	183 (11.5%)	717 (12.7%)	0.89 (0.75;1.06)	0.204	
Adjusted	6,882	170 (11.2%)	667 (12.4%)	0.86 (0.71;1.03)	0.104	2
PS-matched	3,004	169 (11.3%)	183 (12.2%)	0.91 (0.73;1.14)	0.425	3,5
duloxetine discontinuers						
Unadjusted	4,428	183 (11.5%)	272 (9.6%)	1.23 (1.01;1.50)	0.042	
Adjusted	4,208	170 (11.2%)	249 (9.2%)	1.18 (0.95;1.45)	0.133	2
PS-matched	3,008	168 (11.2%)	147 (9.8%)	1.17 (0.93;1.49)	0.184	3,5



Exposure definition: ≥1 redeemed prescription. N: Number of observations in analyses.

OR: Odds ratio for Preterm birth for duloxetine vs. comparators

CI: Wald 95% confidence intervals

Marker 1: Adjusted for data source (Sweden/Denmark), age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, smoking, previous spontaneous abortion, previous stillbirths, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, renal failure, depression, affective, anxiety or phobia, severe stress reaction, diabetic peripheral neuropathic pain, glucose lowering, antihypertensive, fluconazole, estradiol, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination), progesterone (combination), antithyroid (combination).

Marker 2: Adjusted for data source (Sweden/Denmark), age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, smoking, previous spontaneous abortion, previous stillbirths,

gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, depression, affective, anxiety or phobia, severe stress reaction, diabetic peripheral neuropathic pain, glucose lowering, antihypertensive, fluconazole, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination), progesterone (combination).

Marker 3: Conditional logistic regression.

Marker 4: Propensity score based on data source (Sweden/Denmark), age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, smoking, previous spontaneous abortion, previous stillbirths, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, renal failure, depression, affective, anxiety or phobia, severe stress reaction, diabetic peripheral neuropathic pain, glucose lowering, antihypertensive, fluconazole, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination), antithyroid (combination).

Marker 5: Propensity score based on data source (Sweden/Denmark), age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, smoking, previous spontaneous abortion, previous stillbirths, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, renal failure, depression, affective, anxiety or phobia, severe stress reaction, diabetic peripheral neuropathic pain, glucose lowering, antihypertensive, fluconazole, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination).

Sensitivity analyses

Similar patterns were seen in the sensitivity analyses. In the sensitivity analyses where exposed were redefined to overlap between redeemed prescription and exposure time window the association become statistically significant when duloxetine exposed were compared to SSRI exposed. See Supplementary material, Section 2.13.

10.5.14. Preterm birth. Late exposure time window

The incidence rate of preterm birth was 162.2 per 1,000 (95% CI, 128.2-196.3) in women exposed to duloxetine (73 events among 450 exposed women). For the comparator group of duloxetine non-exposed, the incidence rate was 61.1 per 1,000 (95% CI, 60.8-61.4) (corresponding to 127,206 events among 2,082,019 women).

For the other three comparator groups, the incidence rate of preterm birth was 86.6 per 1,000 (95% CI, 83.8-89.5) in women exposed to SSRI (3,241 events among 37,423 exposed women); 159.2 per 1,000 (95% CI, 146.6-171.9) in women exposed to venlafaxine (515 events among 3,234 exposed women) and 96.2 per 1,000 (95% CI, 86.8-105.6) in duloxetine discontinuers (363 events among 3,772 exposed women);

Compared to duloxetine non-exposed unadjusted, adjusted and PS-matched analyses, OR was 2.99 (95% CI, 2.32-3.84), 1.90 (95% CI, 1.44-2.49) and 1.76 (95% CI, 1.28-2.42), respectively.

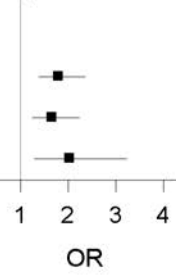
Comparing to the other three comparators SSRI, venlafaxine and duloxetine discontinuers, OR was 1.79 (95% CI, 1.25-2.56); 1.26 (95% CI, 0.86-1.86) and 2.04 (95% CI, 1.29-3.23) for the PS-matched analyses.

An increased risk of preterm birth was observed for women exposed to duloxetine in the late time window compared to duloxetine non-exposed, SSRI exposed and duloxetine discontinuers, found to be statically significant.

When compared to venlafaxine exposed the analyses showed no increased risk.

Preterm birth, Late exposure period. Duloxetine vs four comparators

Comparator	Total N	duloxetine Events(%)	Comparator Events(%)	OR (95% CI)	P-value	Marker
duloxetine non-exposed						
Unadjusted	2,082,469	73 (16.2%)	127,206 (6.1%)	2.99 (2.32;3.84)	1E-17	
Adjusted	1,971,856	65 (15.2%)	116,041 (5.9%)	1.90 (1.44;2.49)	44E-7	1
PS-matched	2,133	64 (15.2%)	161 (9.4%)	1.76 (1.28;2.42)	51E-5	4,5
SSRI						
Unadjusted	37,873	73 (16.2%)	3,241 (8.7%)	2.04 (1.59;2.63)	32E-9	
Adjusted	36,109	65 (15.2%)	2,999 (8.4%)	1.70 (1.29;2.24)	14E-5	2
PS-matched	1,274	64 (15.2%)	78 (9.1%)	1.79 (1.25;2.56)	0.001	4,5
venlafaxine						
Unadjusted	3,684	73 (16.2%)	515 (15.9%)	1.02 (0.78;1.34)	0.871	
Adjusted	3,509	65 (15.2%)	485 (15.7%)	0.92 (0.69;1.24)	0.582	3
PS-matched	849	64 (15.2%)	54 (12.6%)	1.26 (0.86;1.86)	0.24	4,5
duloxetine discontinuers						
Unadjusted	4,250	77 (16.1%)	363 (9.6%)	1.80 (1.38;2.35)	15E-6	
Adjusted	4,038	69 (15.2%)	335 (9.3%)	1.67 (1.24;2.23)	65E-5	3
PS-matched	898	68 (15.2%)	39 (8.7%)	2.04 (1.29;3.23)	0.002	4,5



Exposure definition: ≥1 redeemed prescription. N: Number of observations in analyses.

OR: Odds ratio for Preterm birth for duloxetine vs. comparators

CI: Wald 95% confidence intervals

Marker 1: Adjusted for data source (Sweden/Denmark), age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, smoking, previous spontaneous abortion, previous stillbirths, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, renal failure, depression, affective, anxiety or phobia, severe stress reaction, diabetic peripheral neuropathic pain, glucose lowering, antihypertensive, fluconazole, estradiol, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination), progesterone (combination), antithyroid (combination).

Marker 3: Adjusted for data source (Sweden/Denmark), age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, smoking, previous spontaneous abortion, previous stillbirths, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, depression, affective, anxiety or phobia, severe stress reaction, diabetic peripheral neuropathic pain, glucose lowering,

antihypertensive, fluconazole, thyroid, NSAID, opioids, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination), progesterone (combination).
Marker 4: Conditional logistic regression.
Marker 5: Propensity score based on data source (Sweden/Denmark), age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, smoking, previous spontaneous abortion, previous stillbirths, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, renal failure, depression, affective, anxiety or phobia, severe stress reaction, glucose lowering, antihypertensive, fluconazole, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination).

Sensitivity analyses

In the sensitivity analyses where exposure was redefined to be at least two prescriptions, a similar tendency was observed when duloxetine exposed were compared to duloxetine non-exposed and SSRI exposed, respectively, however, analyses using PS were non-significant. When compared to venlafaxine exposed and duloxetine discontinuers the association was attenuated and statistically non-significant.

In the sensitivity analyses where the cohort was restricted to the first observed pregnancy and when including BMI as covariate, the same patterns were observed, with significant associations in the comparison with duloxetine non-exposed, SSRI exposed and duloxetine discontinuers.

In the sensitivity analyses where exposure was redefined to overlap between redeemed prescriptions and exposure time window (days' supply), the same patterns were observed, however, with reduced associations, and with fewer statistically significant findings.

See Supplementary material, Section 2.14.

10.5.15. Malformation – subtypes

In general, analyses of malformation subtypes were limited due to lack of statistical power.

Because of very few events in the analyses of the following malformation subtype

- Digestive system
- Ear, face and neck
- Eye
- Genital
- Abdominal wall
- Nervous system
- Oro-facial clefts
- Respiratory
- Urinary

the adjusted analyses could not be conducted, and only some of the sensitivity analyses were conducted: The sensitivity analyses where drug exposure was redefined to overlap between redeemed prescription and exposure time window (days' supply), and the sensitivity analyses including BMI as covariate.

Because of the limited number of events, not all models could output p-values for all analyses.

10.5.15.1. Cardiac

The incidence rate of cardiac malformations was 16.5 per 1,000 (95% CI, 10.1-23.0) in women exposed to duloxetine (25 events among 2,074,652 exposed women). For the comparator group of duloxetine non-exposed, the incidence rate was 13.3 per 1,000 (95% CI, 13.1-13.4; 27,508 events among 2,074,652 women).

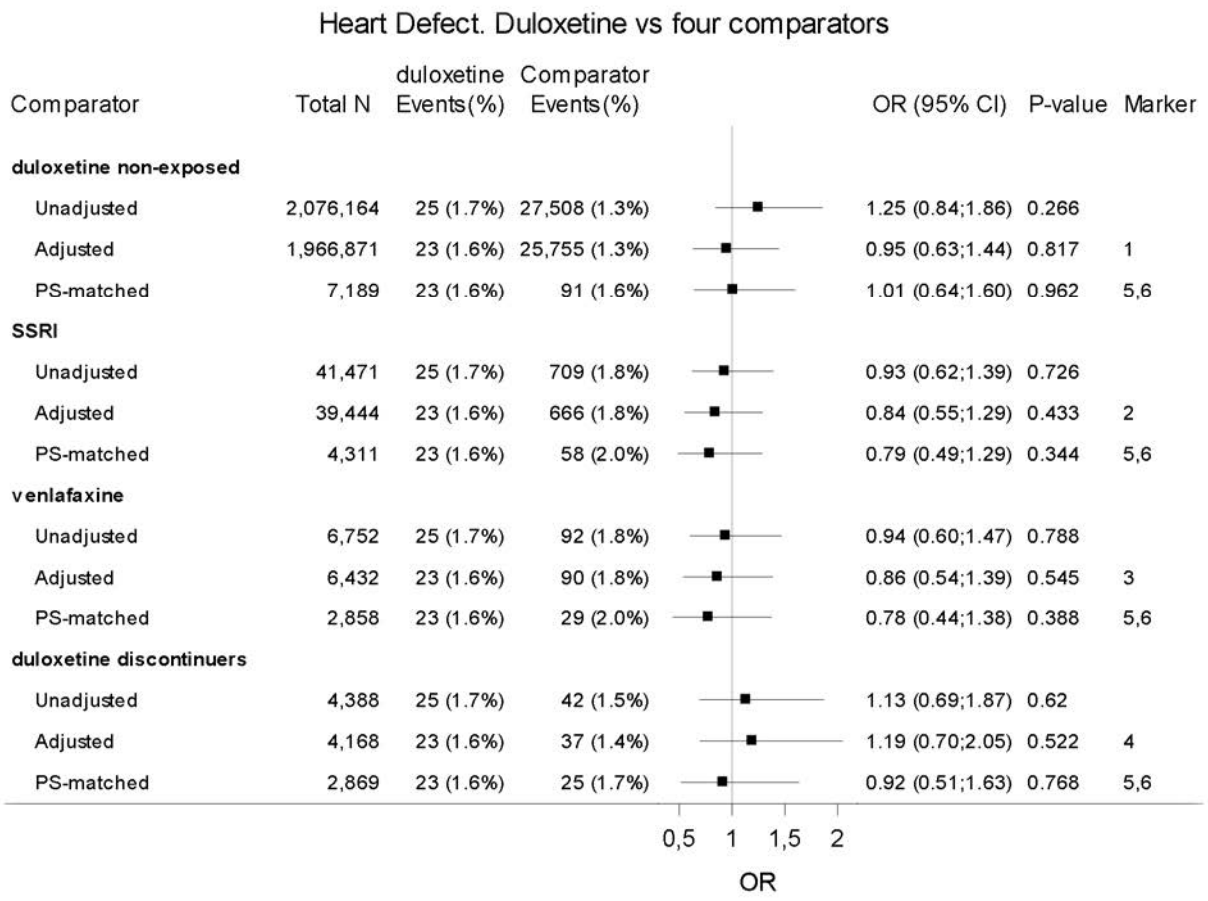
For the other three comparator groups, the incidence rate of cardiac malformations was 17.7 per 1,000 (95% CI, 16.4-19.0) in women exposed to SSRI (709 events among 39,959 exposed women); 17.6 per 1,000 (95% CI, 14.0-21.1) in women exposed to venlafaxine (92 events among 5,240 exposed women) and 14.6 per 1,000 (95% CI, 10.2-19.0) in duloxetine discontinuers (42 events 2,876 exposed women).

Compared to duloxetine non-exposed unadjusted, adjusted and PS-matched analyses, OR was 1.25 (95% CI, 0.84-1.86), 0.95 (95% CI, 0.63-1.44) and 1.01 (95% CI, 0.64-1.60), respectively.

Similar results are obtained comparing to the other three comparators SSRI, venlafaxine and duloxetine discontinuers, where OR was 0.79 (95% CI, 0.49-1.29); 0.78 (95% CI, 0.44-1.29) and 0.92 (95% CI, 0.51-1.63) for the PS-matched analyses.

No association was observed when duloxetine exposed were compared with duloxetine non-exposed.

The point estimates did not suggest an increased risk of cardiac malformations for duloxetine exposed when compared with SSRI exposed and venlafaxine exposed, and an increased risk was observed when compared to duloxetine discontinuers, however, statistically non-significant.



Exposure definition: ≥1 redeemed prescription. N: Number of observations in analyses.

OR: Odds ratio for heart defect for duloxetine vs. comparators

CI: Wald 95% confidence intervals

Marker 1: Adjusted for data source (Sweden/Denmark), age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, smoking, previous spontaneous abortion, previous stillbirths, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, renal failure, depression, affective, anxiety or phobia, severe stress reaction, diabetic peripheral neuropathic pain, glucose lowering, antihypertensive, fluconazole, estradiol, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination), progesterone (combination), antithyroid (combination).

Marker 2: Adjusted for data source (Sweden/Denmark), age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, smoking, previous spontaneous abortion, previous stillbirths, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, renal failure, depression, affective, anxiety or phobia, severe stress reaction, glucose lowering, antihypertensive, fluconazole, estradiol, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination), progesterone (combination), antithyroid (combination).

Marker 3: Adjusted for data source (Sweden/Denmark), age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, smoking, previous spontaneous abortion, previous stillbirths, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, depression, affective, anxiety or phobia, severe stress reaction, glucose lowering, antihypertensive, fluconazole, estradiol, thyroid,

NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination), progesterone (combination).
Marker 4: Adjusted for data source (Sweden/Denmark), age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, smoking, previous spontaneous abortion, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, obesity, depression, affective, anxiety or phobia, severe stress reaction, glucose lowering, antihypertensive, fluconazole, estradiol, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination), progesterone (combination), antithyroid (combination).
Marker 5: Conditional logistic regression.
Marker 6: Propensity score based on data source (Sweden/Denmark), age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, smoking, previous spontaneous abortion, previous stillbirths, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, renal failure, depression, affective, anxiety or phobia, severe stress reaction, diabetic peripheral neuropathic pain, glucose lowering, antihypertensive, fluconazole, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination)

Sensitivity analyses

Similar patterns of no increased risk were observed in the sensitivity analyses. See Supplementary material, Section 3.1.

10.5.15.2. Digestive system

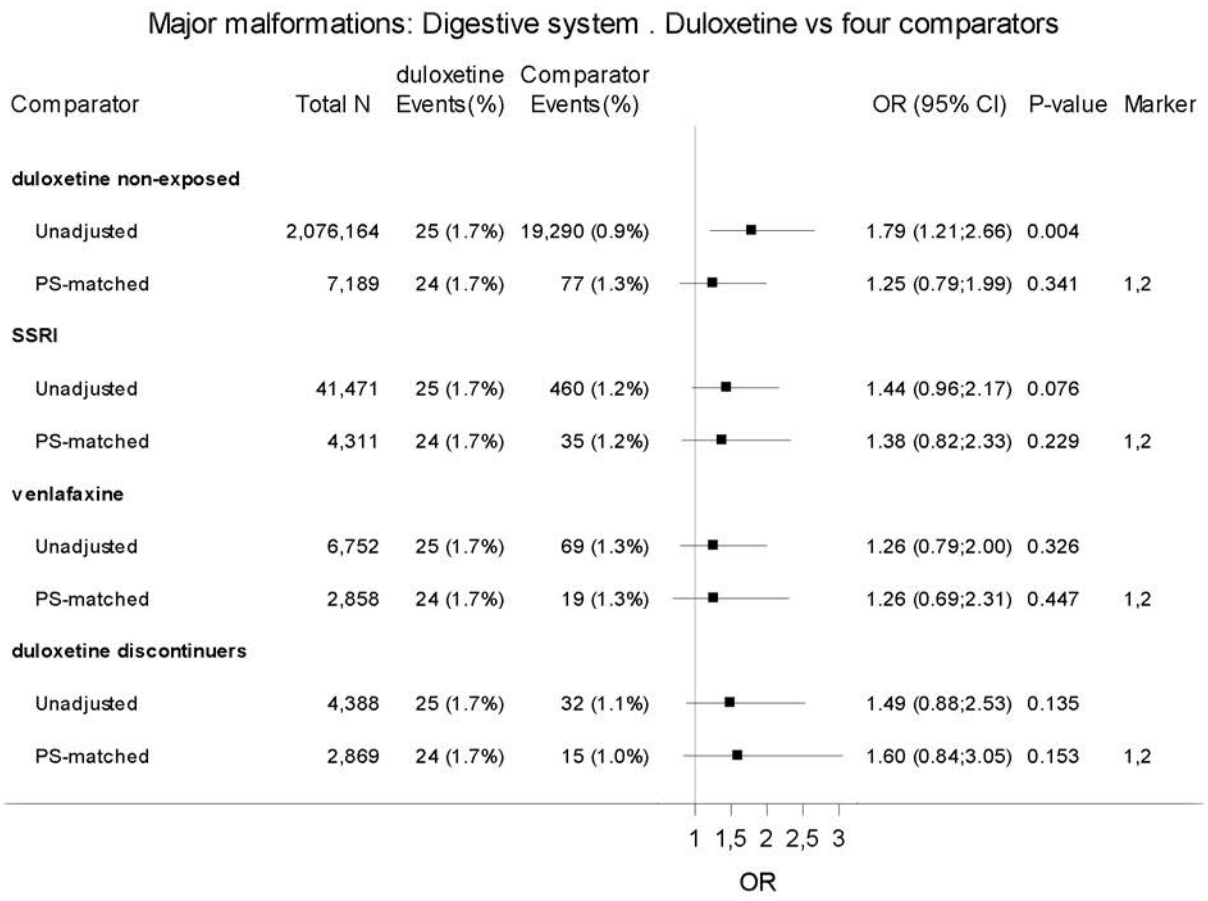
The incidence rate of malformations of the digestive system was 16.5 per 1,000 (95% CI, 10.1-23.0) in women exposed to duloxetine (25 events among 1,512 exposed women). For the comparator group of duloxetine non-exposed, the incidence rate was 9.3 per 1,000 (95% CI, 9.2-9.4) (corresponding to 19,290 events among 2,074,652 women).

For the other three comparator groups, the risk of malformations of the digestive system was 11.5 per 1,000 (95% CI, 10.5-12.6) in women exposed to SSRI (460 events among 39,959 exposed women); 13.2 per 1,000 (95% CI, 10.1-16.3) in women exposed to venlafaxine (69 events among 5,240 exposed women) and 11.1 per 1,000 (95% CI, 7.3-15.0) in duloxetine discontinuers (32 events 2,876 exposed women);

Compared to duloxetine non-exposed unadjusted and PS-matched analyses, ORs were 1.79 (95% CI, 1.21-2.66) and 1.25 (95% CI, 0.79-1.99), respectively.

Similar results are obtained comparing to the other three comparators SSRI, venlafaxine and duloxetine discontinuers, where OR were 1.38 (95% CI, 0.82-2.33); 1.26 (95% CI, 0.69-2.31) and 1.60 (95% CI, 0.84-3.05) for the PS-matched analyses.

The point estimates suggested an increased risk for duloxetine exposed across comparison groups, however, all were with wide confidence intervals and statistically non-significant.



Exposure definition: ≥1 redeemed prescription. N: Number of observations in analyses.

OR: Odds ratio for Major Malformations in the digestive system for duloxetine vs. comparators

CI: Wald 95% confidence intervals

Women who have a redeemed duloxetine prescription 3 months before but not during pregnancy are removed.

Marker 1: Conditional logistic regression.

Marker 2: Propensity score based on data source (Sweden/Denmark), age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, smoking, previous spontaneous abortion, previous stillbirths, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, renal failure, depression, affective, anxiety or phobia, severe stress reaction, diabetic peripheral neuropathic pain, glucose lowering, antihypertensive, fluconazole, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination).

Marker 3: Propensity score based on data source (Sweden/Denmark), age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, smoking, previous spontaneous abortion, previous stillbirths, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, renal failure, depression, affective, anxiety or phobia, severe stress reaction, diabetic peripheral neuropathic pain, glucose lowering, antihypertensive, fluconazole, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination) , BMI (grouped).

Sensitivity analyses

A similar pattern was observed in the sensitivity analyses, but with an exception in the sensitivity analyses where exposure is redefined to overlap between redeemed prescriptions and exposure time window. Here, the increased risk for duloxetine exposed when compared to duloxetine discontinuers became statistically significant. See Supplementary material, Section 3.2

10.5.15.3. Ear, face and neck

The incidence rate of genital malformations was 4.0 per 1,000 (95% CI, 0.8-7.1) in women exposed to duloxetine (6 events among 1,512 exposed women). For the comparator group of duloxetine non-exposed, the incidence rate was 2.4 per 1,000 (95% CI, 2.3-2.4) (corresponding to 4,912 events among 2,074,652 women).

For the other three comparator groups, the incidence rate of genital malformations was 2.5 per 1,000 (95% CI, 2.0-3.0) in women exposed to SSRI (101 events among 39,959 exposed women); 1.9 per 1,000 (95% CI, 0.7-3.1) in women exposed to venlafaxine (10 events among 1,512 exposed women). There were less than 5 events among duloxetine discontinuers, which does not allow for any incidence rate calculations.

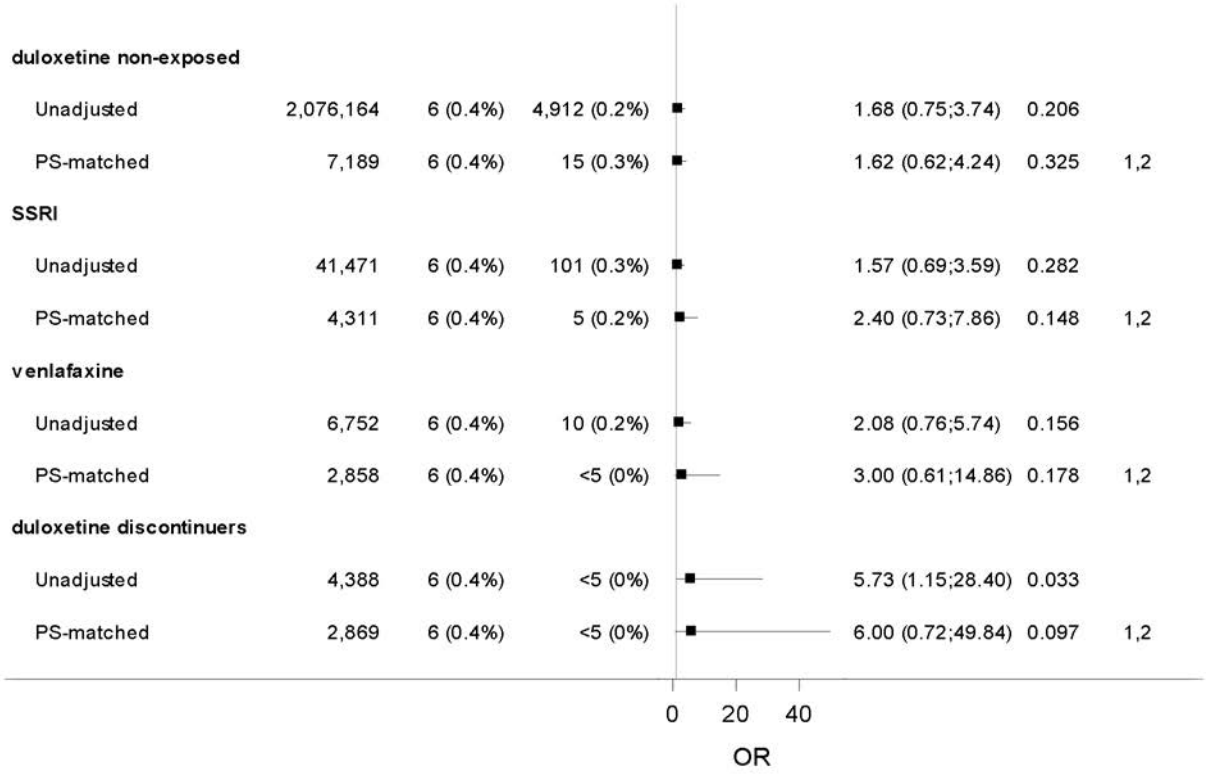
Compared to duloxetine non-exposed unadjusted and PS-matched analyses, ORs were 1.68 (95% CI, 0.75-3.74) and 1.62 (95% CI, 0.62-4.24), respectively.

Comparing to the other three comparators SSRI and venlafaxine, ORs were 2.40 (95% CI, 0.71-7.86) and 3.00 (95% CI, 0.29-2.55) for the PS-matched analyses.

The point estimates suggested an increased risk for duloxetine exposed across comparison groups but were with wide confidence intervals and statistically non-significant.

Major Malformations in the Ear Face and Neck . Duloxetine vs four comparators

Comparator	Total N	duloxetine Events(%)	Comparator Events(%)	OR (95% CI)	P-value	Marker
duloxetine non-exposed						
Unadjusted	2,076,164	6 (0.4%)	4,912 (0.2%)	1.68 (0.75;3.74)	0.206	
PS-matched	7,189	6 (0.4%)	15 (0.3%)	1.62 (0.62;4.24)	0.325	1,2
SSRI						
Unadjusted	41,471	6 (0.4%)	101 (0.3%)	1.57 (0.69;3.59)	0.282	
PS-matched	4,311	6 (0.4%)	5 (0.2%)	2.40 (0.73;7.86)	0.148	1,2
venlafaxine						
Unadjusted	6,752	6 (0.4%)	10 (0.2%)	2.08 (0.76;5.74)	0.156	
PS-matched	2,858	6 (0.4%)	<5 (0%)	3.00 (0.61;14.86)	0.178	1,2
duloxetine discontinuers						
Unadjusted	4,388	6 (0.4%)	<5 (0%)	5.73 (1.15;28.40)	0.033	
PS-matched	2,869	6 (0.4%)	<5 (0%)	6.00 (0.72;49.84)	0.097	1,2



Exposure definition: ≥1 redeemed prescription. N: Number of observations in analyses.

OR: Odds ratio for Major Malformations in the ear, face or neck for duloxetine vs. comparators

CI: Wald 95% confidence intervals

Women who have a redeemed duloxetine prescription 3 months before but not during pregnancy are removed.

Marker 1: Conditional logistic regression.

Marker 2: Propensity score based on data source (Sweden/Denmark), age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, smoking, previous spontaneous abortion, previous stillbirths, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, renal failure, depression, affective, anxiety or phobia, severe stress reaction, diabetic peripheral neuropathic pain, glucose lowering, antihypertensive, fluconazole, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination).

Marker 3: Propensity score based on data source (Sweden/Denmark), age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, smoking, previous spontaneous abortion, previous stillbirths, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, renal failure, depression, affective, anxiety or phobia, severe stress reaction, diabetic peripheral neuropathic pain, glucose lowering, antihypertensive, fluconazole, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination) , BMI (grouped).

Sensitivity analyses

A similar pattern was observed in the sensitivity analyses. See Supplementary material, Section 3.3.

10.5.15.4. Eye

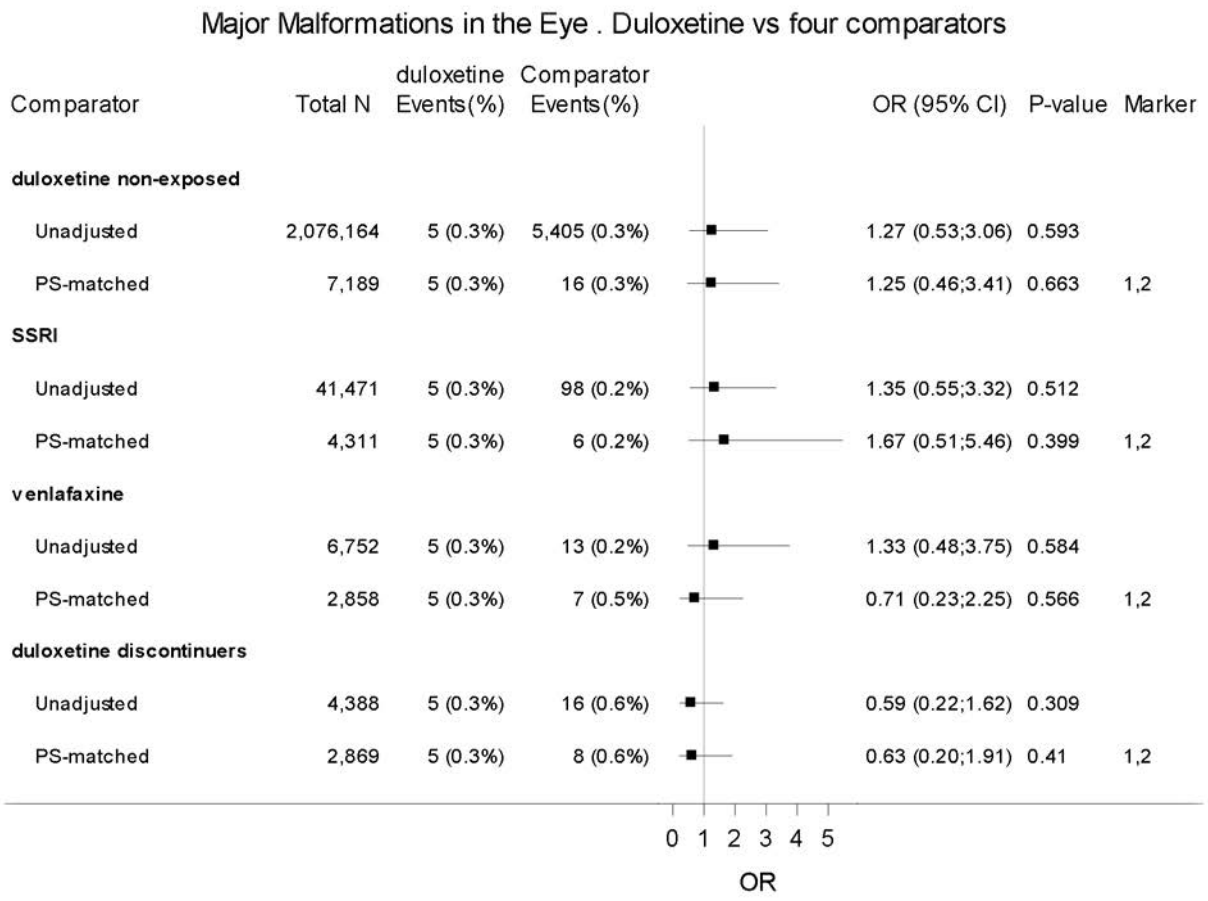
The incidence rate of malformations of the eye was 3.3 per 1,000 (95% CI, 0.4-6.2) in women exposed to duloxetine (5 events among 1,512 exposed women). For the comparator group of duloxetine non-exposed, the incidence rate was 2.6 per 1,000 (95% CI, 2.5-2.7) (corresponding to 5,405 events among 2,074,652 women).

For the other three comparator groups, the incidence rate of genital malformations was 2.5 per 1,000 (95% CI, 2.0-2.9) in women exposed to SSRI (98 events among 39,959 exposed women); 2.5 per 1,000 (95% CI, 1.1-3.8) in women exposed to venlafaxine (13 events among 5,240 exposed women) and 5.6 per 1,000 (95% CI, 2.8-8.3) in duloxetine discontinuers (16 events 2,876 exposed women);

Compared to duloxetine non-exposed unadjusted and PS-matched analyses, ORs were 1.27 (95% CI, 0.53-3.06) and 1.25 (95% CI, 0.46-3.41), respectively.

Comparing to the other three comparators SSRI, venlafaxine and duloxetine discontinuers, where OR were 1.67 (95% CI, 0.51-6.46); 0.71 (95% CI, 0.23-2.25) and 0.63 (95% CI, 0.20-1.91) for the PS-matched analyses.

The point estimates suggested an increased risk for duloxetine exposed when compared to duloxetine non-exposed, SSRI exposed and venlafaxine-exposed, but all are with wide confidence intervals and statistically non-significant. When compared to duloxetine discontinuers no increased risk was seen.



Exposure definition: ≥1 redeemed prescription. N: Number of observations in analyses.

OR: Odds ratio for Major Malformations in the Eye for duloxetine vs. comparators

CI: Wald 95% confidence intervals

Women who have a redeemed duloxetine prescription 3 months before but not during pregnancy are removed.

Marker 1: Conditional logistic regression.

Marker 2: Propensity score based on data source (Sweden/Denmark), age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, smoking, previous spontaneous abortion, previous stillbirths, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, renal failure, depression, affective, anxiety or phobia, severe stress reaction, diabetic peripheral neuropathic pain, glucose lowering, antihypertensive, fluconazole, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination).

Marker 3: Propensity score based on data source (Sweden/Denmark), age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, smoking, previous spontaneous abortion, previous stillbirths, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, renal failure, depression, affective, anxiety or phobia, severe stress reaction, diabetic peripheral neuropathic pain, glucose lowering, antihypertensive, fluconazole, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination) , BMI (grouped).

Sensitivity analyses

In the sensitivity analyses no increased risk was seen for the PS-matched analyses where exposure is redefined to overlap between redeemed prescriptions and exposure time window as well as in the analysis including BMI as a covariate. See Supplementary material, Section 3.4

10.5.15.5. Genital malformations

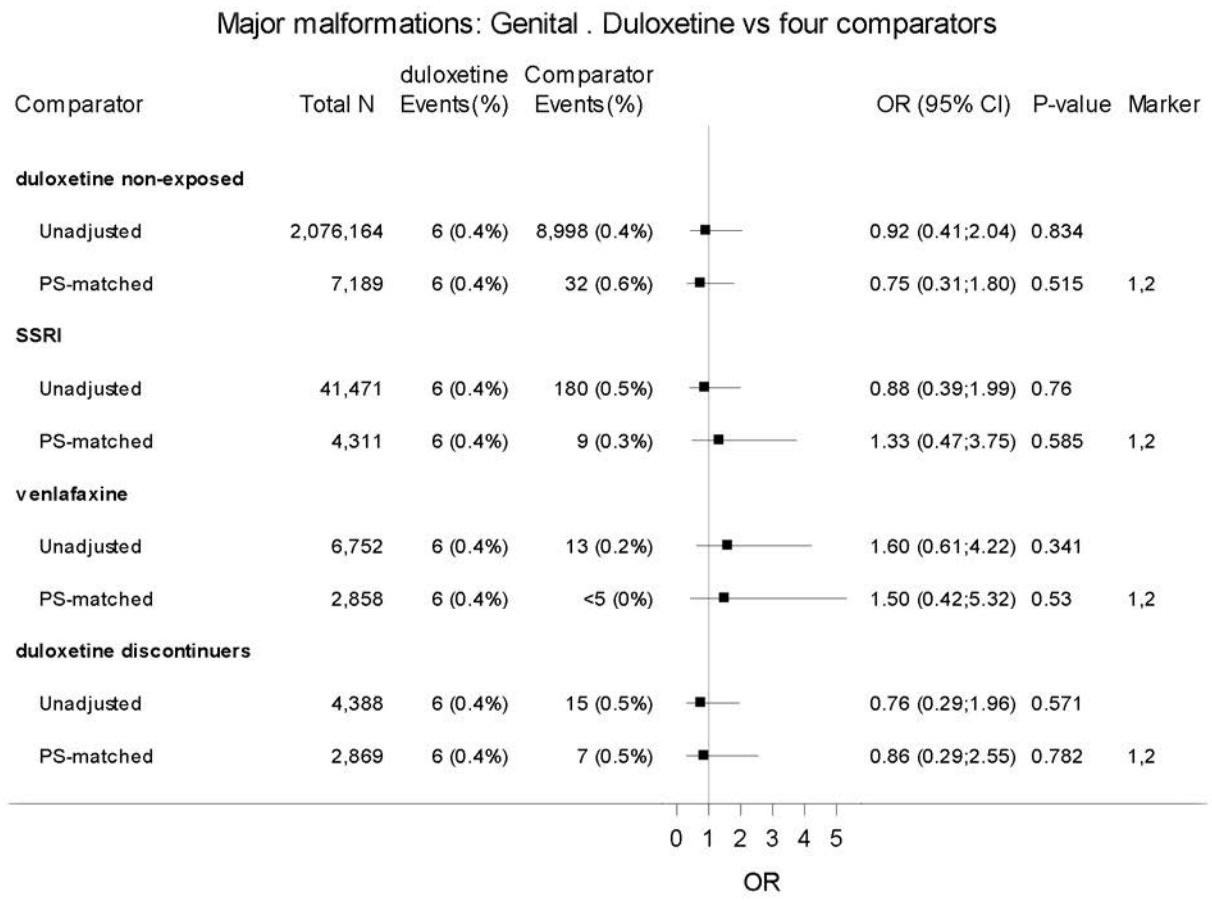
The incidence rate of genital malformations was 4.0 per 1,000 (95% CI, 0.8-7.1) in women exposed to duloxetine (6 events among 1,512 exposed women). For the comparator group of duloxetine non-exposed, the risk was 4.3 per 1,000 (95% CI, 4.2-4.4) (corresponding to 8.998 events among 2,074,652 women).

For the other three comparator groups, the incidence rate of genital malformations was 4.5 per 1,000 (95% CI, 3.8-5.2) in women exposed to SSRI (180 events among 39,959 exposed women); 2.5 per 1,000 (95% CI, 1.1-3.8) in women exposed to venlafaxine (13 events among 5,240 exposed women) and 5.2 per 1,000 (95% CI, 2.6-7.8) in duloxetine discontinuers (15 events 2,876 exposed women);

Compared to duloxetine non-exposed unadjusted and PS-matched analyses, ORs were 0.92 (95% CI, 0.41-2.04) and 0.75 (95% CI, 0.31-1.80), respectively.

Comparing to the other three comparators SSRI, venlafaxine and duloxetine discontinuers, where ORs were 1.33 (95% CI, 0.47-3.75); 1.50 (95% CI, 0.42-5.32) and 0.86 (95% CI, 0.29-2.55) for the PS-matched analyses.

The point estimates suggested no increased risk for duloxetine exposed when compared to duloxetine non-exposed, SSRI exposed and duloxetine discontinuers, and an increased risk when compared with venlafaxine exposed. However, the association was statistically non-significant and with wide confidence intervals.



Exposure definition: ≥1 redeemed prescription. N: Number of observations in analyses.

OR: Odds ratio for Major Malformations in the genital for duloxetine vs. comparators

CI: Wald 95% confidence intervals

Women who have a redeemed duloxetine prescription 3 months before but not during pregnancy are removed.

Marker 1: Conditional logistic regression.

Marker 2: Propensity score based on data source (Sweden/Denmark), age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, smoking, previous spontaneous abortion, previous stillbirths, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, renal failure, depression, affective, anxiety or phobia, severe stress reaction, diabetic peripheral neuropathic pain, glucose lowering, antihypertensive, fluconazole, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination).

Marker 3: Propensity score based on data source (Sweden/Denmark), age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, smoking, previous spontaneous abortion, previous stillbirths, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, renal failure, depression, affective, anxiety or phobia, severe stress reaction, diabetic peripheral neuropathic pain, glucose lowering, antihypertensive, fluconazole, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination) , BMI (grouped).

Sensitivity analyses

In the sensitivity analyses where exposure is redefined to overlap between redeemed prescriptions, and in the analyses including BMI as covariate, the estimates showed no increased risk of genital malformations. See Supplementary material, Section 3.5.

10.5.15.6. Abdominal wall

There were less than 5 events of abdominal wall malformations among duloxetine exposed which does not allow to publish the incidence rate. For the comparator group of duloxetine non-exposed, the incidence rate was 0.3 per 1,000 (95% CI, 0.2-0.3) (corresponding to 531 events among 2,074,652 women).

Point estimates have wide confidence intervals and were either statistical non-significant or the analyses could not obtain a p-value. This does not allow for a clear interpretation.

Major Malformations: Abdominal wall defects . Duloxetine vs four comparators

Comparator	Total N	duloxetine Events(%)	Comparator Events(%)	OR (95% CI)	P-value	Marker
duloxetine non-exposed						
Unadjusted	2,076,164	<5 (0%)	531 (0.0%)	5.19 (1.29;20.77)	0.02	
PS-matched	7,189	<5 (0%)	<5 (0%)	2.00 (0.37;10.92)	0.423	1,2
SSRI						
Unadjusted	41,471	<5 (0%)	20 (0.1%)	2.65 (0.62;11.33)	0.19	
PS-matched	4,311	<5 (0%)	<5 (0%)	4.00 (0.36;44.11)	0.258	1,2
venlafaxine						
Unadjusted	6,752	<5 (0%)	<5 (0%)	416E3 (0.00;94E212)	0.958	
PS-matched	2,858	<5 (0%)	<5 (0%)	416E3 (0.00;94E212)		1,2
duloxetine discontinuers						
Unadjusted	4,388	<5 (0%)	<5 (0%)	174E3 (0.00;15E186)	0.955	
PS-matched	2,869	<5 (0%)	<5 (0%)	174E3 (0.00;15E186)		1,2

Exposure definition: ≥1 redeemed prescription. N: Number of observations in analyses.

OR: Odds ratio for Major Malformations in the abdominal wall for duloxetine vs. comparators

CI: Wald 95% confidence intervals

Women who have a redeemed duloxetine prescription 3 months before but not during pregnancy are removed.

Marker 1: Conditional logistic regression.

Marker 2: Propensity score based on data source (Sweden/Denmark), age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, smoking, previous spontaneous abortion, previous stillbirths, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, renal failure, depression, affective, anxiety or phobia, severe stress reaction, diabetic peripheral neuropathic pain, glucose lowering, antihypertensive, fluconazole, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination).

Marker 3: Propensity score based on data source (Sweden/Denmark), age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, smoking, previous spontaneous abortion, previous stillbirths, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, renal failure, depression, affective, anxiety or phobia, severe stress reaction, diabetic peripheral neuropathic pain, glucose lowering, antihypertensive, fluconazole, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination) , BMI (grouped).

Sensitivity analyses

Similar patterns were seen in the sensitivity analyses. See Supplementary material, Section 3.6.

10.5.15.7. Limb

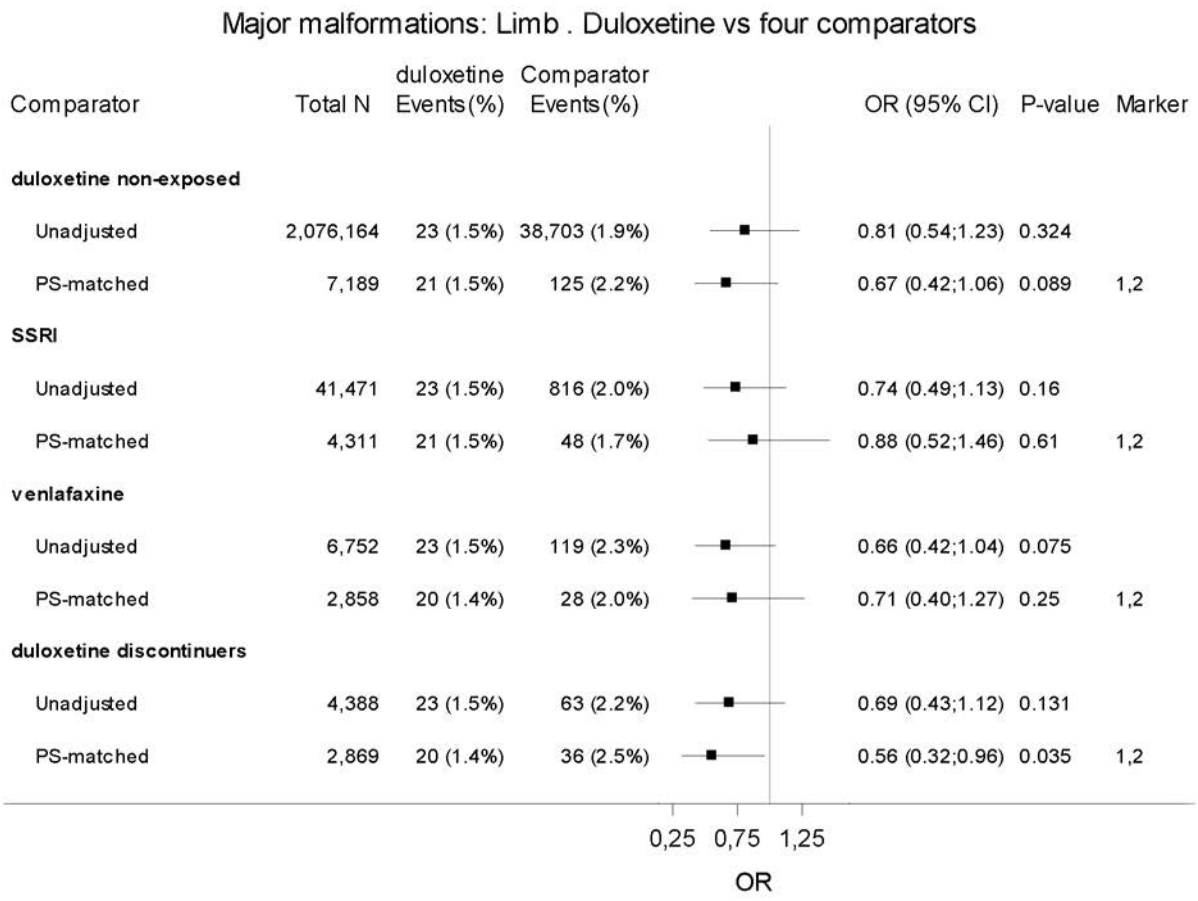
The incidence rate of limb malformations was 15.2 per 1,000 (95% CI, 9.0-21.4) in women exposed to duloxetine (23 events among 1,512 exposed women). For the comparator group of duloxetine non-exposed, the incidence rate was 18.7 per 1,000 (95% CI, 18.5-18.8) (corresponding to 38,703 events among 2,074,652 women).

For the other three comparator groups, the incidence rate of limb malformations was 20.4 per 1,000 (95% CI, 19.0-21.8) in women exposed to SSRI (816 events among 39,959 exposed women); 22.7 per 1,000 (95% CI, 18.7-26.7) in women exposed to venlafaxine (119 events among 5,240 exposed women) and 21.9 per 1,000 (95% CI, 16.6-27.3) in duloxetine discontinuers (63 events 2,876 exposed women);

Compared to duloxetine non-exposed unadjusted and PS-matched analyses, ORs were 0.81 (95% CI, 0.54-1.23) and 0.67 (95% CI, 0.42-1.06), respectively.

Similar results are obtained comparing to the other three comparators SSRI, venlafaxine and duloxetine discontinuers, where ORs were 0.88 (95% CI, 0.52-1.46); 0.71 (95% CI, 0.40-1.27) and 0.56 (95% CI, 0.32-0.96) for the PS-matched analyses.

Point estimates suggest no increased risk for duloxetine exposed across comparison groups.



Exposure definition: ≥1 redeemed prescription. N: Number of observations in analyses.

OR: Odds ratio for Major Malformations in the limb for duloxetine vs. comparators

CI: Wald 95% confidence intervals

Women who have a redeemed duloxetine prescription 3 months before but not during pregnancy are removed.

Marker 1: Conditional logistic regression.

Marker 2: Propensity score based on data source (Sweden/Denmark), age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, smoking, previous spontaneous abortion, previous stillbirths, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, renal failure, depression, affective, anxiety or phobia, severe stress reaction, diabetic peripheral neuropathic pain, glucose lowering, antihypertensive, fluconazole, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination).

Marker 3: Propensity score based on data source (Sweden/Denmark), age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, smoking, previous spontaneous abortion, previous stillbirths, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, renal failure, depression, affective, anxiety or phobia, severe stress reaction, diabetic peripheral neuropathic pain, glucose lowering, antihypertensive, fluconazole, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination) , BMI (grouped).

Sensitivity analyses

The sensitivity analyses showed the same patterns with no associations. See Supplementary material, Section 3.7.

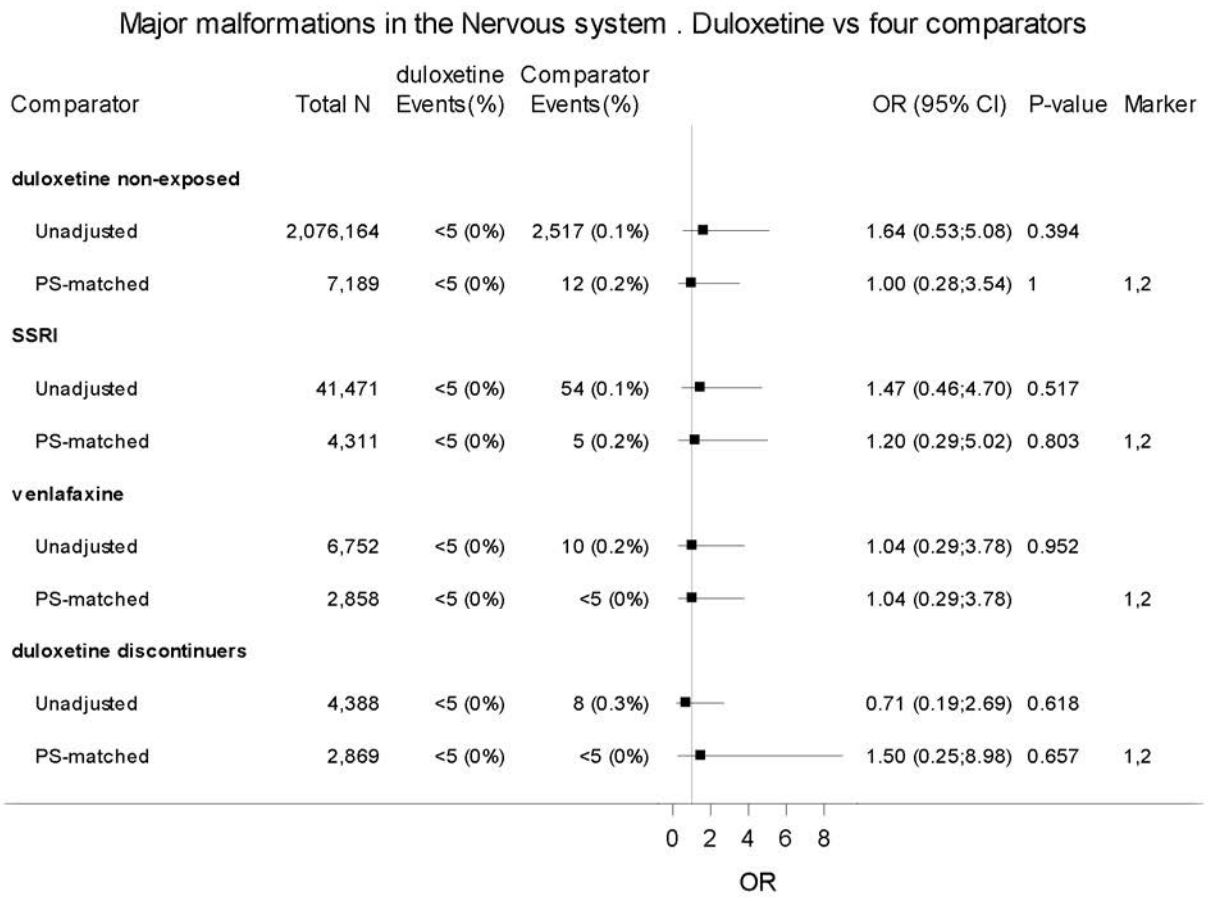
10.5.15.8. Nervous system

There were less than 5 events of malformations of the nervous system among duloxetine exposed which does not allow for the incidence rate to be published. For the comparator group of duloxetine non-exposed, the incidence rate was 1.2 per 1,000 (95% CI, 1.2-1.3) (corresponding to 2,517 events among 2,074,652 women).

Compared to duloxetine non-exposed unadjusted and PS-matched analyses, ORs were 1.64 (95% CI, 0.53-5.08) and 1.00 (95% CI, 0.28-3.54), respectively.

Comparing to the other three comparators SSRI, venlafaxine and duloxetine discontinuers, ORs were 1.20 (95% CI, 0.29-5.02); 1.04 (95% CI, 0.29-3.78) and 1.50 (95% CI, 0.25-8.98) for the PS-matched analyses.

Point estimates suggested a slight increased risk for duloxetine compared to non-exposed and SSRI-exposed, however, confidence intervals were wide, and statistically non-significant.



Exposure definition: ≥1 redeemed prescription. N: Number of observations in analyses.

OR: Odds ratio for Major Malformations in the nervous system for duloxetine vs. comparators

CI: Wald 95% confidence intervals

Women who have a redeemed duloxetine prescription 3 months before but not during pregnancy are removed.

Marker 1: Conditional logistic regression.

Marker 2: Propensity score based on data source (Sweden/Denmark), age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, smoking, previous spontaneous abortion, previous stillbirths, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, renal failure, depression, affective, anxiety or phobia, severe stress reaction, diabetic peripheral neuropathic pain, glucose lowering, antihypertensive, fluconazole, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination).

Marker 3: Propensity score based on data source (Sweden/Denmark), age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, smoking, previous spontaneous abortion, previous stillbirths, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, renal failure, depression, affective, anxiety or phobia, severe stress reaction, diabetic peripheral neuropathic pain, glucose lowering, antihypertensive, fluconazole, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination) , BMI (grouped).

Sensitivity analyses

The sensitivity analyses showed the same patterns with wide and statistically non-significant confidence intervals. See Supplementary material Section 3.8.

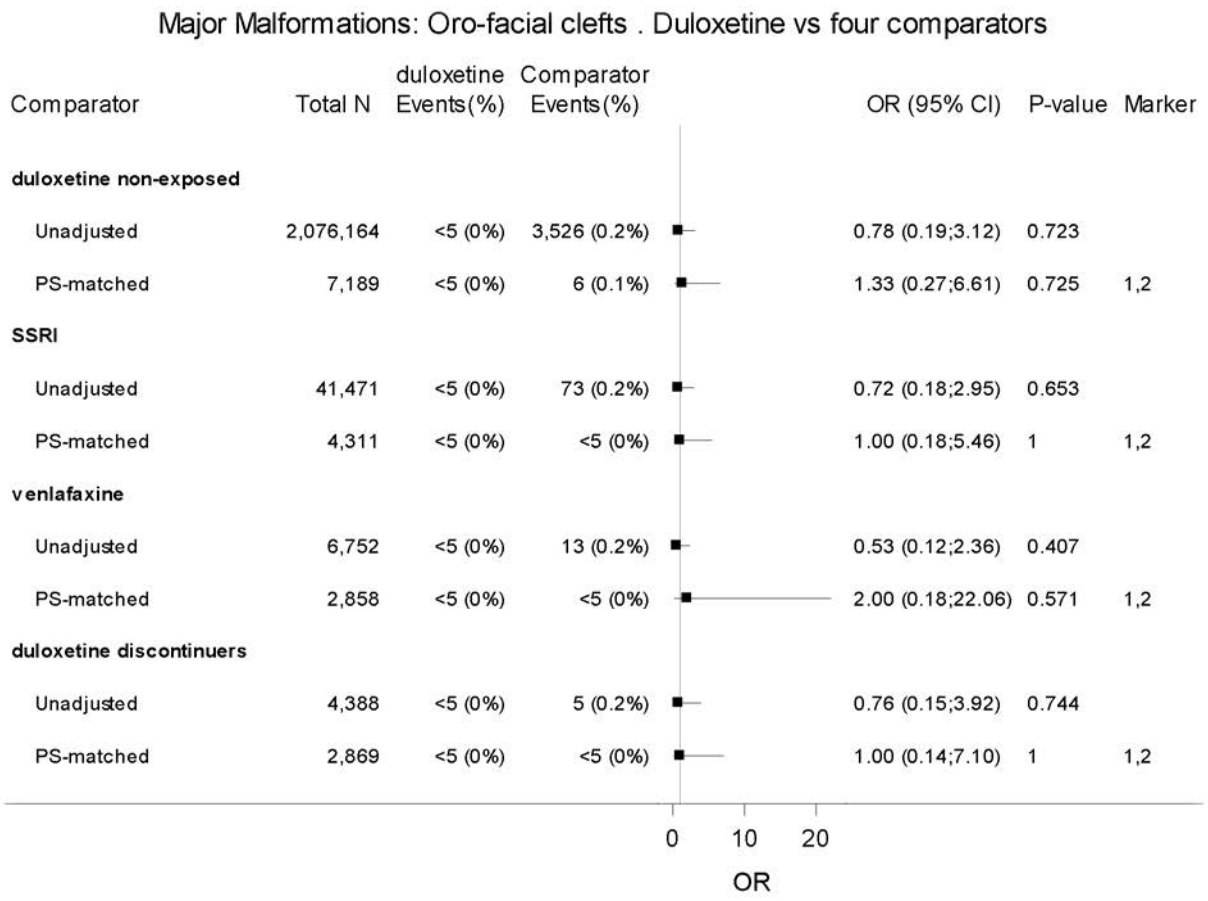
10.5.15.9. Oro-facial clefts

There were less than 5 events of oro-facial cleft malformations among duloxetine exposed which does not allow for the incidence rate to be published. For the comparator group of duloxetine non-exposed, the incidence rate was 1.7 per 1,000 (95% CI, 1.6-1.8) (corresponding to 3,526 events among 2,074,652 women).

Compared to duloxetine non-exposed unadjusted and PS-matched analyses, ORs were 0.78 (95% CI, 0.19-3.12) and 1.33 (95% CI, 0.27-6.61), respectively.

Comparing to the other three comparators SSRI, venlafaxine and duloxetine discontinuers, ORs were 1.00 (95% CI, 0.18-5.46); 2.00 (95% CI, 0.18-22.06) and 1.00 (95% CI, 0.14-7.10) for the PS-matched analyses.

Point estimates suggested no increased risk for duloxetine exposed across comparison groups.



Exposure definition: ≥1 redeemed prescription. N: Number of observations in analyses.

OR: Odds ratio for Major Malformations in the oro-facial clefts for duloxetine vs. comparators

CI: Wald 95% confidence intervals

Women who have a redeemed duloxetine prescription 3 months before but not during pregnancy are removed.

Marker 1: Conditional logistic regression.

Marker 2: Propensity score based on data source (Sweden/Denmark), age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, smoking, previous spontaneous abortion, previous stillbirths, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, renal failure, depression, affective, anxiety or phobia, severe stress reaction, diabetic peripheral neuropathic pain, glucose lowering, antihypertensive, fluconazole, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination).

Marker 3: Propensity score based on data source (Sweden/Denmark), age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, smoking, previous spontaneous abortion, previous stillbirths, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, renal failure, depression, affective, anxiety or phobia, severe stress reaction, diabetic peripheral neuropathic pain, glucose lowering, antihypertensive, fluconazole, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination) , BMI (grouped).

Sensitivity analyses

Similar patterns were seen in the sensitivity analyses. See Supplementary material Section 3.9.

10.5.15.10. Respiratory

There were less than 5 events of respiratory malformations among duloxetine exposed which does not allow for the incidence rate to be published. For the comparator group of duloxetine non-exposed, the incidence rate was 1.3 per 1,000 (95% CI, 1.3-1.4) (corresponding to 2,720 events among 2,074,652 women).

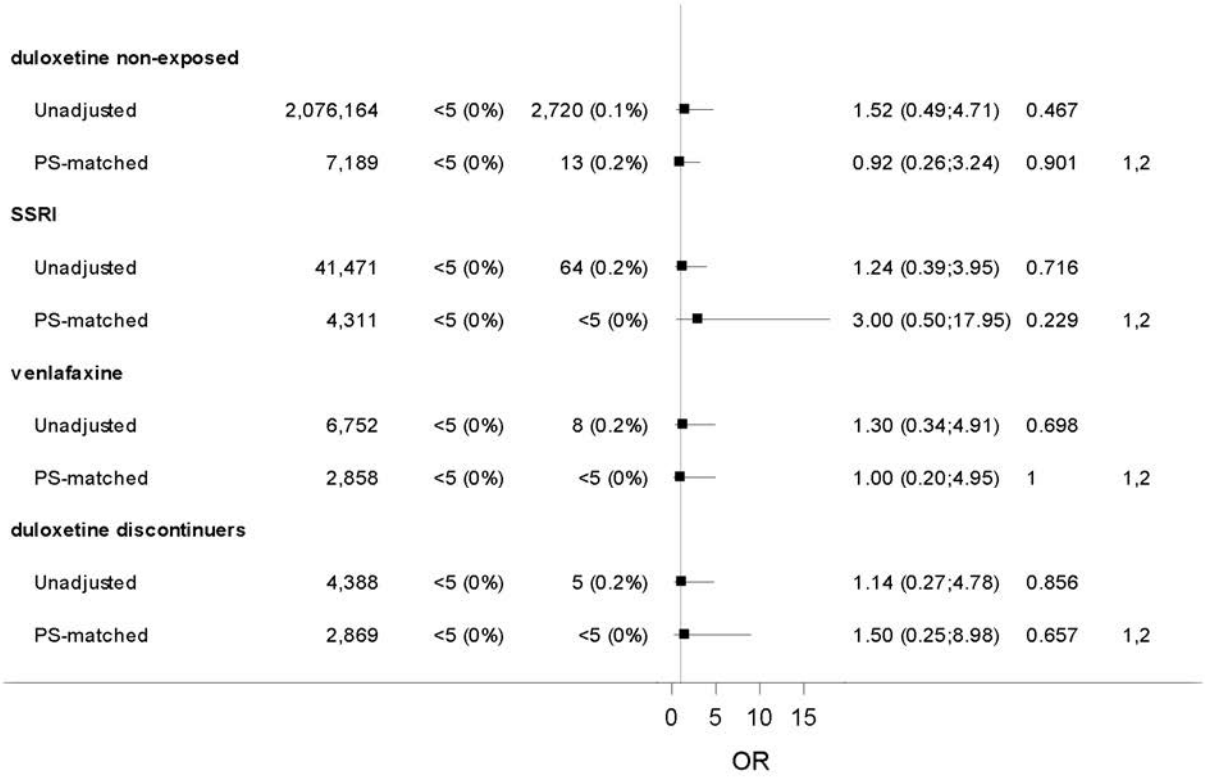
Compared to duloxetine non-exposed unadjusted and PS-matched analyses, ORs were 1.52 (95% CI, 0.49-4.71) and 0.92 (95% CI, 0.26-3.24), respectively.

Comparing to the other three comparators SSRI, venlafaxine and duloxetine discontinuers, ORs were 3.00 (95% CI, 0.50-17.95); 1.00 (95% CI, 0.20-4.95) and 1.50 (95% CI, 0.25-8.98) for the PS-matched analyses.

Analyses suggest no increased risk for duloxetine exposed across comparison groups. The analyses were performed with a low number of events.

Major malformations: Respiratory . Duloxetine vs four comparators

Comparator	Total N	duloxetine Events(%)	Comparator Events(%)	OR (95% CI)	P-value	Marker
duloxetine non-exposed						
Unadjusted	2,076,164	<5 (0%)	2,720 (0.1%)	1.52 (0.49;4.71)	0.467	
PS-matched	7,189	<5 (0%)	13 (0.2%)	0.92 (0.26;3.24)	0.901	1,2
SSRI						
Unadjusted	41,471	<5 (0%)	64 (0.2%)	1.24 (0.39;3.95)	0.716	
PS-matched	4,311	<5 (0%)	<5 (0%)	3.00 (0.50;17.95)	0.229	1,2
venlafaxine						
Unadjusted	6,752	<5 (0%)	8 (0.2%)	1.30 (0.34;4.91)	0.698	
PS-matched	2,858	<5 (0%)	<5 (0%)	1.00 (0.20;4.95)	1	1,2
duloxetine discontinuers						
Unadjusted	4,388	<5 (0%)	5 (0.2%)	1.14 (0.27;4.78)	0.856	
PS-matched	2,869	<5 (0%)	<5 (0%)	1.50 (0.25;8.98)	0.657	1,2



Exposure definition: ≥1 redeemed prescription. N: Number of observations in analyses.
OR: Odds ratio for Major Malformations in the respiratory system for duloxetine vs. comparators
CI: Wald 95% confidence intervals
Women who have a redeemed duloxetine prescription 3 months before but not during pregnancy are removed.
Marker 1: Conditional logistic regression.
Marker 2: Propensity score based on data source (Sweden/Denmark), age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, smoking, previous spontaneous abortion, previous stillbirths, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, renal failure, depression, affective, anxiety or phobia, severe stress reaction, diabetic peripheral neuropathic pain, glucose lowering, antihypertensive, fluconazole, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination).
Marker 3: Propensity score based on data source (Sweden/Denmark), age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, smoking, previous spontaneous abortion, previous stillbirths, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, renal failure, depression, affective, anxiety or phobia, severe stress reaction, diabetic peripheral neuropathic pain, glucose lowering, antihypertensive, fluconazole, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination) , BMI (grouped).

Sensitivity analyses

The sensitivity analyses showed the same patterns, of no increased risk. See Supplementary material, Section 3.10.

10.5.15.11. Urinary tract

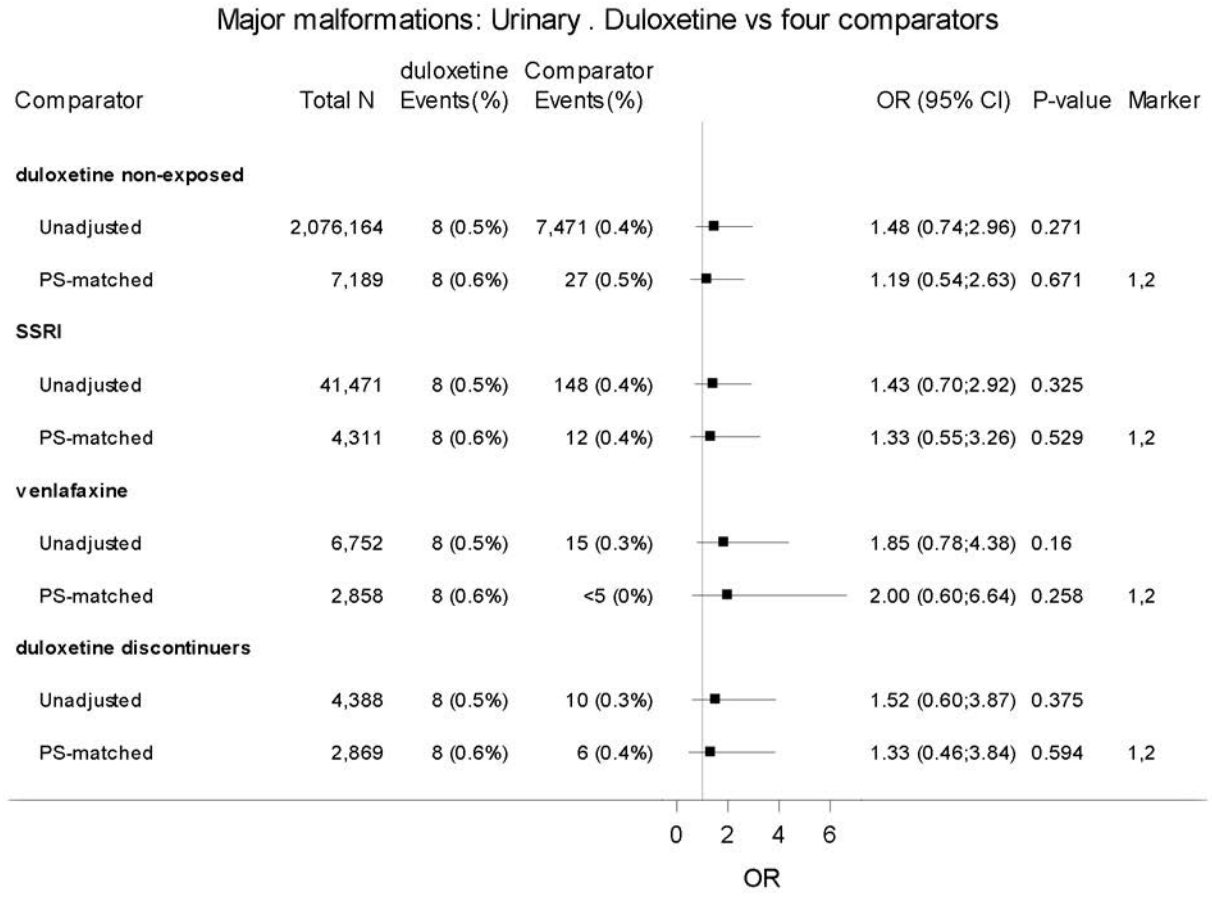
The incidence rate of urinary tract malformations was 5.3 per 1,000 (95% CI,1.6-8.9) in women exposed to duloxetine (8 events among 1,512 exposed women). For the comparator group of duloxetine non-exposed, the incidence rate was 3.6 per 1,000 (95% CI, 3.5-3.7) (corresponding to 7,471 events among 2,074,652 women).

For the other three comparator groups, the incidence rate of urinary tract malformations was 3.7 per 1,000 (95% CI, 3.1-4.3) in women exposed to SSRI (148 events among 39,959 exposed women); 2.9 per 1,000 (95% CI,1.4-4.3) in women exposed to venlafaxine (15 events among 5,240 exposed women) and 3.5 per 1,000 (95% CI, 1.3-5.6) in duloxetine discontinuers (10 events among 2,876 exposed women);

Compared to duloxetine non-exposed unadjusted and PS-matched analyses, ORs were 1.48 (95% CI, 0.74-2.96) and 1.19 (95% CI, 0.54-2.63), respectively.

Similar results are obtained comparing to the other three comparators SSRI, venlafaxine and duloxetine discontinuers, where ORs were 1.33 (95% CI, 0.55-3.26); 2.00 (95% CI, 0.60-6.64) and 1.33 (95% CI, 0.46-3.84) for the PS-matched analyses.

In conclusion, point estimates suggested an increased risk for duloxetine exposed across comparison groups, however, the confidence intervals were wide, and statistically non-significant.



Exposure definition: ≥1 redeemed prescription. N: Number of observations in analyses.

OR: Odds ratio for Major Malformations in the urinary tract for duloxetine vs. comparators

CI: Wald 95% confidence intervals

Women who have a redeemed duloxetine prescription 3 months before but not during pregnancy are removed.

Marker 1: Conditional logistic regression.

Marker 2: Propensity score based on data source (Sweden/Denmark), age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, smoking, previous spontaneous abortion, previous stillbirths, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, renal failure, depression, affective, anxiety or phobia, severe stress reaction, diabetic peripheral neuropathic pain, glucose lowering, antihypertensive, fluconazole, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination).

Marker 3: Propensity score based on data source (Sweden/Denmark), age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, smoking, previous spontaneous abortion, previous stillbirths, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, renal

failure, depression, affective, anxiety or phobia, severe stress reaction, diabetic peripheral neuropathic pain, glucose lowering, antihypertensive, fluconazole, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination) , BMI (grouped).

Sensitivity analyses

Similar patterns were seen in the sensitivity analyses. See Supplementary material, Section 3.11.

10.5.15.12. Other anomalies/syndromes

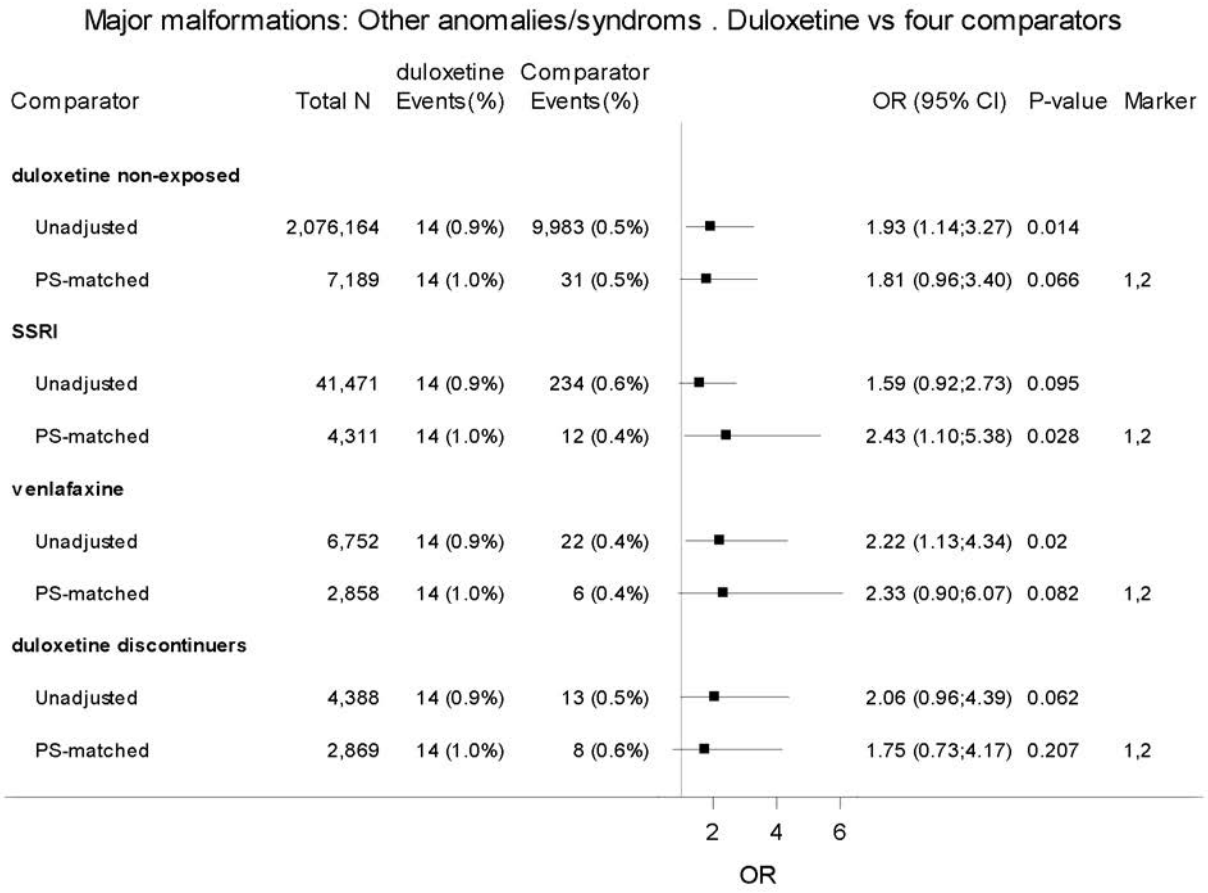
The incidence rate of other anomalies/syndromes was 9.3 per 1,000 (95% CI, 4.4-14.1) in women exposed to duloxetine (14 events among 1.512 exposed women). For the comparator group of duloxetine non-exposed, the incidence rate was 4.8 per 1,000 (95% CI, 4.7-4.9) (corresponding to 9,983 events among 2,074,652 women).

For the other three comparator groups, the incidence rate of other anomalies/syndromes was 5.9 per 1,000 (95% CI, 5.1-6.6) in women exposed to SSRI (234 events among 39,959 exposed women); 4.2 per 1,000 (95% CI, 2.4-5.9) in women exposed to venlafaxine (22 events among 5,240 exposed women) and 4.5 per 1,000 (95% CI, 2.1-7) in duloxetine discontinuers (13 events among 2,876 exposed women);

Compared to duloxetine non-exposed unadjusted and PS-matched analyses, ORs were 1.93 (95% CI, 1.14-3.27) and 1.81 (95% CI, 0.96-3.40), respectively.

Similar results are obtained comparing to the other three comparators SSRI, venlafaxine and duloxetine discontinuers, where ORs were 2.43 (95% CI, 1.10-5.38); 2.33 (95% CI, 0.90-6.07) and 0.80 (95% CI, 0.73-4.17) for the PS-matched analyses.

Point estimates suggested an increased risk which was statistically significant in the unadjusted analyses comparing duloxetine exposed to duloxetine non-exposed and venlafaxine exposed. Results also showed an increased risk in the PS-matched analysis when compared to SSRI-exposed. Due to the low number of events, the confidence intervals were wide.



Exposure definition: ≥1 redeemed prescription. N: Number of observations in analyses.

OR: Odds ratio for Major Malformations of other anomalies/syndromes for duloxetine vs. comparators

CI: Wald 95% confidence intervals

Women who have a redeemed duloxetine prescription 3 months before but not during pregnancy are removed.

Marker 1: Conditional logistic regression.

Marker 2: Propensity score based on data source (Sweden/Denmark), age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, smoking, previous spontaneous abortion, previous stillbirths, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, renal failure, depression, affective, anxiety or phobia, severe stress reaction, diabetic peripheral neuropathic pain, glucose lowering, antihypertensive, fluconazole, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination).

Marker 3: Propensity score based on data source (Sweden/Denmark), age (grouped), education (grouped), household income, year (grouped), psychiatric hospital, psychiatric outpatient, smoking, previous spontaneous abortion, previous stillbirths, gestational diabetes during index pregnancy, diabetes, hyper or hypothyroidism, hypertension, obesity, renal failure, depression, affective, anxiety or phobia, severe stress reaction, diabetic peripheral neuropathic pain, glucose lowering, antihypertensive, fluconazole, thyroid, NSAID, opioids, triptans, antiepileptics, antipsychotics, anxiolytics, corticosteroid (combination) , BMI (grouped).

Sensitivity analyses

A similar pattern was seen in the sensitivity analyses with tendency to an increased risk for duloxetine exposed across comparison groups. In the sensitivity analyses where exposure was redefined to overlap between redeemed prescriptions and exposure time window (days' supply), the comparison with duloxetine non-exposed and SSRI exposed was statistically significant. In the sensitivity analyses including BMI as covariate, the comparison with venlafaxine-exposed was statistically significant. See Supplementary material, Section 3.12.

10.6. Other analyses

No other analyses have been performed.

10.7. Adverse events/adverse reactions

When the register data are used for research purposes, the possible findings cannot be used for decisions concerning individual patients. The national prescription databases in Denmark and Sweden cannot be used for treatment of individual patients or supervision of individual prescribers' prescribing patterns.

As a cohort study using retrospective data, individual case level reporting on adverse events/adverse reaction is not applicable.

11. Discussion

11.1. Key results

Table 11.1 shows the main results of the study based on the PS matched analyses. Statistically significant results are marked in bold. The estimates are commented in the sections below.

Table 11.1 Summary of main results - propensity score matched analyses *

Outcome	Duloxetine non-exposed	SSRIs exposed	venlafaxine exposed	duloxetine discontinuers
Major malformations	0.98 (0.74;1.30)	1.07 (0.78;1.46)	0.95 (0.66;1.36)	0.80 (0.56;1.14)
Minor malformations	1.09 (0.82;1.45)	**1.39 (1.00;1.94)**	1.20 (0.82;1.76)	1.11 (0.77;1.60)
Spontaneous abortions (cox)	1.08 (0.89;1.31)	**1.25 (1.00;1.57)**	1.08 (0.82;1.41)	0.99 (0.76;1.30)
Spontaneous abortions (logistic regression)	1.02 (0.84;1.24)	1.18 (0.95;1.47)	1.10 (0.85;1.42)	0.95 (0.73;1.23)
Elective abortions	**1.41 (1.25;1.59)**	**1.32 (1.15;1.51)**	1.09 (0.93;1.27)	**1.46 (1.23;1.75)**
Stillbirths	0.71 (0.28;1.85)	0.83 (0.29;2.37)	1.00 (0.29;3.45)	1.00 (0.29;3.45)
SGA early exposure	0.83 (0.69;1.01)	0.96 (0.77;1.18)	1.18 (0.91;1.52)	0.96 (0.75;1.23)
SGA late exposure	0.70 (0.47;1.05)	**0.57 (0.38;0.87)**	1.58 (0.89;2.81)	0.73 (0.45;1.17)
Preterm early exposure	**1.33 (1.10;1.60)**	1.21 (0.99;1.47)	0.91 (0.73;1.14)	1.17 (0.93;1.49)
Preterm late exposure	**1.76 (1.28;2.42)**	**1.79 (1.25;2.56)**	1.26 (0.86;1.86)	**2.04 (1.29;3.23)**

*Propensity score was based on maternal education, age, comorbidity, comedication, hospital contacts (somatic and psychiatric), year of pregnancy and family income. For non-abortion outcomes the propensity score was also based on maternal smoking, previous spontaneous abortion and stillbirths.

11.1.1. Major congenital malformations

No increased risk for the primary outcome major congenital malformation was observed for duloxetine exposed compared to any of the four comparator groups: Duloxetine non-exposed, SSRI exposed, venlafaxine exposed and duloxetine discontinuers. This was the case for both unadjusted, adjusted and PS matched analyses.

11.1.2. Minor congenital malformations

Similar results were observed for minor congenital malformations, though for the unadjusted analyses comparing duloxetine exposed with duloxetine non-exposed and SSRI exposed, respectively, showed increased estimates. However, in the adjusted and PS matched analyses the associations became statistically non-significant or very close to non-significant. As no association was found in the unadjusted analyses comparing duloxetine exposed with venlafaxine exposed, this could indicate that the unadjusted analysis comparing with duloxetine non-exposed and SSRI exposed is confounded by the indication or is affected by another unmeasured confounder, which was included (directly or indirectly) in the adjusted models.

11.1.3. Spontaneous abortions

For spontaneous abortions, the main analyses showed an increased risk when comparing duloxetine exposed with SSRI exposed. No association was found when comparing with unexposed, exposed to venlafaxine and duloxetine discontinuers. The sensitivity analyses showed increased risks when restricting the cohort to the first observed pregnancy in the study period. When redefining exposure to more than one prescription, the association was strengthened and increased for comparison with SSRI exposed and venlafaxine exposed. There was no association with unexposed and discontinuers. When calculating days' supply and redefining exposure to days overlapping exposure time window, there were no associations with the four comparator groups.

11.1.4. Elective abortions

For elective abortions, most of the analyses pointed towards an increased hazard around 40% for women exposed to duloxetine. An exception was the PS matched analysis comparing duloxetine exposed to venlafaxine exposed where the increased hazard decreased to around 10%, which was borderline significant. The sensitivity analyses redefining exposure to at least two redeemed prescriptions support the increased hazard, also for the comparison with venlafaxine exposed. However, in the comparison with duloxetine discontinuers, no association was found. The median length of pregnancy before termination was 55.5 days for duloxetine exposed, 55.0 for duloxetine discontinuers and 56.0 for the remaining comparison groups. These results could indicate that elective abortions among duloxetine exposed were not performed due to adverse findings in the fetus.

11.1.5. Stillbirths

All analyses estimating the risk of stillbirth for women exposed to duloxetine suggest no increased risk. The results were consistent across comparison groups and in the sensitivity analyses.

11.1.6. Small for gestational age (SGA)

For SGA, all findings suggest no increased risk across comparison groups, whether the exposure period is early or late in pregnancy, or the cohorts are stratified for congenital malformations.

11.1.7. Preterm birth

A statistically significant increased risk of preterm birth for early exposure to duloxetine was found compared with duloxetine non-exposed, after adjusting for risk factors. However, when compared to SSRI exposed the increased risk disappeared in the adjusted and PS matched

analyses indicated that the increased risk could be affected by confounding by indication. No increased risk compared to venlafaxine exposed before and after adjustment was observed.

For preterm birth for women exposed to duloxetine in the late exposure period, a graduating decreased risk across comparison with duloxetine non-exposed and SSRI exposed, which remained statistically significant. When comparing duloxetine with duloxetine discontinuers, assessed in the late exposure period, an increased risk was found. No increased risk compared to venlafaxine exposed was observed.

11.1.8. Subtypes of malformations

For subtypes of malformation, the analyses were generally influence by lack of power with few events. Despite point estimates suggesting different associations for the various malformation subtypes, all analyses were associated with large statistical uncertainty which did not allow for certain conclusions. It is of note that a statistically significant increased risk of "other anomalies and syndromes" was found. This must be interpreted with caution based on the low number of cases (n=14). Furthermore, no increased risk of cardiac malformations was found, which is in contrast to some studies suggesting an increased risk for other antidepressants, like SSRIs.

11.2. Limitations

The national health registers are unique due to their completeness and follow-up time. They are recognized internationally, and widely used for epidemiological studies of a wide variety of medical issues. Data is gathered prospectively, but analyses are made retrospectively. It has to be noted that the main purpose of the data collection is for clinical use, and not for research. The main limitations are therefore centered around the potential for misclassification and unmeasured confounders.

11.2.1. Exposure misclassification.

Exposure was defined by the redemption of a prescription. Although the medication has been prescribed, dispensed, redeemed and paid for, there is a probability that the patient did not ingest the drug. In the sensitivity analyses, a stricter definition was used by requiring that women had to redeem >1 prescription, under the assumption that filling multiple prescriptions increases the likelihood that the medication was taken as prescribed. This change of exposure definition did not have a significant impact on the majority of results. There was no risk of recall bias given that data was not based on interviews and the prescription registers included more than 98% of all redeemed prescription at community pharmacies.(136) There was no risk of false negatives given that duloxetine is not available OTC, and therefore recorded in the registers by law.

Drug exposure during hospital stay: There is no information on the women's drug exposure during hospital stays, as this is not recorded in any available registers. This might have led to misclassification of exposure. However, less than 10% of pregnant women had a hospital contact within 1 year before pregnancy.

The comparison groups were not mutually exclusive, i.e. duloxetine non-exposed could have been exposed to an SSRI. This has no impact on the unadjusted and adjusted analyses since the number of exposed to an SSRI or venlafaxine among the non-exposed is negligible. It could, however, have an impact on the PS-matched analyses where 16% were exposed to an SSRI and 3% to venlafaxine among the duloxetine non-exposed. Hence, the duloxetine non-exposed were not a comparison group not exposed to antidepressant. However, since the adjusted and PS-matched analyses do not differ significantly, the potential impact was not present solely in the PS-matched analyses and suggest that this possible limitation had minimal impact.

Concurrent antidepressant medication was not used as covariates in neither the adjusted analyses nor the PS models. This was to avoid potential collinearity. From the baseline tables, it is evident that concurrent antidepressant medication is present. Since concurrent antidepressant medication was not used as covariates, the potential impact on the outcome is not addressed in the individual analyses.

11.2.2. Outcome misclassification

The outcomes chosen for the present study have been used in multiple previous published peer reviewed studies.(66,85,87,137,138) The outcomes have a high positive predictive value and are regarded as having a high validity. The quality of the malformation diagnoses has been validated and found to have a predictive value of 88% for having a congenital malformation, with a completeness of 90%. Any misclassification of the diagnoses is most probably random, and not attributable to a specific drug exposure.(101) Diagnoses of heart defects have been validated in another study and have been found to have a positive predictive value of 98.4.(116) Furthermore, in Denmark, the diagnosis of spontaneous abortions has been validated and found to have a positive predictive value of 97.4.(100) Regardless of this, some potential for outcome misclassification remains. This might apply for the diagnosis of spontaneous abortions. Using registers to analyze the risk of abortion, like in the present study, does not allow for identification of the earliest abortions unrecognized by the women. They are not recorded in the registers, since they did not lead to a hospital contact. Symptoms of an early spontaneous abortion may be perceived as a late menstrual period or dealt with in the primary care system (outside the hospital system). Denmark and Sweden have free, universal health care, which leads to the number of spontaneous abortions treated outside the hospital system decreasing with increased gestational age. Hypothetically, the risk of the outcome will be underestimated if the exposure (i.e. duloxetine) specifically is associated with early abortions and therefore lead to information bias. (139) If women experiencing an abortion do not chose to contact a hospital, the number of

registered abortions would be underestimated. Studies have shown that the underreporting is 25% and is probably the result of abortions in the early pregnancy.(117) If women with exposure to duloxetine during pregnancy were more likely to report an abortion than women in the comparator groups, it could have led to a false increased risk of the outcome. There is, however, no scientific evidence corroborating this, nor did was found any signs of bias when investigating the timing of spontaneous abortions.

The available registers do not hold information on congenital malformations for abortions and stillbirths. This could have led to underestimation of congenital malformations. It is believed that this theoretical increased risk would has partly been caught in the analyses of spontaneous abortions. This limitation could, however, explain the increased risk associated with elective abortions.

No information on emergency contraception (i.e. morning-after pill) was obtained. If women exposed to duloxetine were more prone to taking the morning-after pill, it could decrease the rate of pregnancies and registered abortions. This needs to be further analyzed in future studies.

11.2.3. Unmeasured confounders

Information on potentially confounding lifestyle factors such as alcohol and drug abuse/dependence were not available. Information on smoking, and to a certain extent BMI was available. In the present study, there was adjusted for socioeconomic status (education and income) and smoking. Since smoking and low socioeconomic status is associated with alcohol and drug abuse, it is assumed that there is indirectly adjusted for these missing confounders due to their close association. Other important unmeasured confounders are the indication for treatment with an antidepressant, and the severity of depression, which can lead to confounding by indication. In addition, there can be other health conditions, not available through the registers, related to patients treated with duloxetine. Several comparison groups of women using different types of antidepressants and a comparison group of discontinuers were used, which helped to detangle the effect of medications from the underlying maternal illness.

11.2.4. Other limitations

- OTC medication and illicit drugs: Information was not recorded on an individual basis in the available registers, if they were not prescribed. OTC medications include analgesics as acetaminophen and ibuprofen, non-sedating antihistamines, antacids and vitamin supplements. These drugs are only sold in small packages (<10 pills) without a prescription, and therefore mainly used for short treatment periods. Hence, exposure to OTC drugs was expected to be strong confounders, and missing information on OTC medications was expected to have very limited impact on the study. Illicit drug use could be a confounder in the present analyses, since women exposed to duloxetine could have a

higher risk of taking illicit drugs than non-exposed. If these illicit drugs are associated with the studied outcomes, it could skew the results towards a higher risk of the outcomes for duloxetine exposed. However, there is no reason to believe that women exposed to duloxetine have a higher risk of taking illicit drugs than women exposed to SSRIs or venlafaxine. The present analyses using these groups as comparators would therefore capture this possible confounder.

- Breastfeeding: The available registers did not have reliable information on breastfeeding. Plans of breastfeeding could in theory influence choice of antidepressant before pregnancy, whereby influencing the results. This has not been analyzed in the present study.
- Low statistical power: Some of the outcomes in the present study are rare (e.g. neonatal mortality, specific congenital malformations). Although the size of the cohort is considerable (n=2,132,940), there was limited statistical power to detect small increases in risk or risks associated with rare outcomes (e.g. stillbirth). The absolute numbers need to be taken into consideration when determining whether the risk estimates are clinically relevant.
- Completeness of diagnosis for depressive disorder: Patient diagnoses are only recorded in the national registers if the patient has had contact with a hospital. Depressive disorder (especially mild and moderate) is most often treated in the primary sector, without contact to the secondary sector (i.e. hospitals). Hence, it is probable that the relative low number of recorded diagnoses is due to most patients redeeming a prescription for duloxetine, or any other antidepressant, not having a recorded diagnosis, and the indication for their treatment is therefore an assumption. This also applies to other diagnoses mainly treated in the primary sector, e.g. diabetes, hypertension, mild infections, migraine, mild /moderate pain.
- Indication of treatment: Indication of drug treatment was not available. Apart from major depressive episode, duloxetine is indicated to treat neuropathic pain and anxiety. In the present study, it was assumed that most women exposed to duloxetine were in treatment for depression. A misclassification might have led to lack of inclusion of relevant confounding factors in the analyses. The present analyses strived to account for this by comparing exposure to duloxetine with exposure to venlafaxine, that has similar indications. Duloxetine might also have been used off-label, of which there was no information.
- Emigration: All women emigrating during the study period were removed to ensure follow-up time. If emigration was associated with the exposure, it could have affected the estimates. This is found highly unlikely.

Since the national health registers from Denmark and Sweden cover the whole nation, there is minimal risk of selection bias. However, if one of the independent variables in the model is associated leads directly to the outcome and is an underlying cause of the exposure, there is a risk of selection bias.

11.3. Interpretation

Compared to other antidepressants, like SSRIs and venlafaxine, there are few studies concerning the safety of duloxetine. (90,94,98,140–142) A review from 2015, concluded that there were insufficient data on duloxetine to draw definitive conclusions about its safety in pregnancy or lactation (143). Therefore, the present study adds needed information to the available knowledge. The main finding is that there is no increased risk of major and minor congenital malformations for offspring of women exposed to duloxetine during the first trimester. This result is in line with previous studies (90,94,140,142) and case-reports (91,97,144) analyzing this association.

The results were corroborated in a systematic review from 2016. It concluded that among women exposed to duloxetine during the first trimester (n=668), there was no increased risk of congenital malformations, with an OR (95% confidence interval) of 0.80 (0.46-1.29).(98)

In pooled data from eight placebo controlled clinical trials (basis of the original drug application for duloxetine in the treatment of major depressive disorder), 28 pregnancies were exposed to duloxetine in the first trimester (dose range 40-120 mg/day, mean exposure 49.5 days). There were no malformations reported in any of these cases.(142) The study by Einarson et al (140), published as a preliminary report, compared 208 pregnant women to women exposed to other antidepressant and women not exposed to teratogenic drugs. The analyses showed no increased risk of congenital malformations (p=0.992). Another study, by Hoog et al., based on the Lilly Safety System (a post-marketing surveillance system) and the FDA Adverse Events Reporting System (AERS), found that the risk for major malformations was comparable to the historic control rates in the general population (2–3%).(90) In the present study, a risk of 43.0 per 1,000 (95% CI, 32.8 – 53.2) (65 events among 1,512 exposed women)was found among duloxetine exposed and 38.9 per 1,000 (95% CI, 38.6 – 39.2) (80,695 events among 2,074,652 women) among non-exposed (see tables in Section 10.5.1). The risks are slightly higher than in the study by Hoog et al. that can be attributed to differences in registration and definition of congenital malformations between Denmark and Sweden, and the US. A descriptive study of the rate of congenital malformations based on the Swedish Medical Birth Registry found no increased risk of congenital malformations among duloxetine exposed with an OR (95% confidence interval) of 0.80 (0.32–1.64). The present study includes considerably more exposed women (n=1,512) and further adjustments were made to account for possible confounders. None of the mentioned studies adjusted for smoking and BMI and performed PS matched analyses and sensitivity analyses like the present study. Based on the present results and the available evidence, it is safe to conclude that there is no association between exposure to duloxetine during the first trimester of pregnancy and congenital malformations overall.

In addition, the present study analyzed associations between duloxetine exposure and specific malformation subtypes. The estimates did not indicate a possible increased risk, based on available data. The number of cases was low, and estimates were therefore associated with great statistical uncertainty. It must be noted that a statistically significant increased risk of “other anomalies and syndromes” was found. This must be interpreted with caution based on the low

number of cases (n=14) and the wide confidence intervals, as well as the multiple comparisons which can lead to false positive estimates. Furthermore, there is no pharmacological mechanisms that can explain the association. It has been suggested that observational studies, as the present, might be influenced by detection bias since women suffering from depression or anxiety are more likely to attend medical care with their offspring compared to healthy women. (145,146) This might lead to an increased probability of disease detection and diagnosis assignment. This result is therefore attributed to be a chance finding.

The number of studies analyzing the risk of spontaneous abortions is limited. (90,141) The study by Hoog et al. (90) reported 41 miscarriages among 233 pregnancies exposed to duloxetine (17.6%). As with malformations, the rate was interpreted to be similar to the background population in the study;12% - 15% in the US population.(147) This study is limited by few cases, and has no control group.

A study based on the Danish Medical Birth Registry analyzed the risk of spontaneous abortions for women exposed to an antidepressant and found an increased risk. The risk, however, was attributed to confounding by indication. (141) When stratifying for specific antidepressants, treatment with duloxetine was associated with an increased risk of spontaneous abortion with an unadjusted relative risk of 2.12 (95% CI 1.52-2.96) compared to pregnancies with no duloxetine prescriptions and 3.12 (95% CI 1.55-6.31) when analyzing pregnancies with a diagnosis of depression.

The primary adjusted analyses of the present study where exposure was defined as one or more redeemed prescriptions showed an increased risk of spontaneous abortions when comparing duloxetine exposed to SSRI exposed. There was, however, not found an increased risk compared to non-exposed, venlafaxine exposed, and duloxetine discontinuers. This is in contrast with the previously mentioned study based on Danish data (141). The present study differs from the study by Kjaersgaard et al. when it comes to study period, adjustment and cohort size. Kjaersgaard et al. included pregnancies between 1997 and 2008, whilst the present study includes the period 2004-2016. Furthermore, the estimates in Kjaersgaard et al.'s study were not adjusted for potential confounders, and very few (numbers not available) pregnancies were exposed to duloxetine. The present analyses of adjusted estimates are based on a large cohort of over 1,500 exposed pregnancies, which increases the validity of the primary results. However, the sensitivity analyses showed different trends depending on the definition of exposure and choice of cohort:

In the sensitivity analyses defining exposure as more than one redeemed prescription during pregnancy, showed an increased risk for duloxetine exposed compared to SSRI exposed and venlafaxine exposed. In these sensitivity analyses, the exposure is more likely since women redeemed multiple prescriptions compared to the primary analyses where women were to redeem only one prescription. These results might therefore compare cohorts with more reliable exposure definitions but will also exclude women who were exposed but only redeemed one prescription (false negatives). The increased risk might be attributed to exposure to duloxetine. This was, however, not supported by the findings of no increased risk when comparing to duloxetine non-exposed where an increased risk would be expected.

On the other hand, redeeming multiple prescriptions could be associated with disease severity. This possible explanation is strengthened by the results showing the same risk for women exposed to duloxetine and those discontinuing treatment before pregnancy. Women discontinuing treatment might be comparable with the duloxetine exposed group, except for their redemption of duloxetine prescriptions during pregnancy. However, from the baseline table, it is seen that 21% of the women discontinuing duloxetine had prescription of SSRI indicating less depression severity. An unmeasured confounder might therefore be responsible for the increased risk found when comparing to SSRI and venlafaxine exposed. Duloxetine exposed might differ in unmeasured factors, e.g. depression severity, from SSRI and discontinuers that could be associated with the analyzed outcome. The present study strives to adjust for depression severity by adjusting for depressive disorder diagnosis, number of psychiatric hospital visits and psychiatric outpatient visits. The diagnosis of depressive disorder is only given if a patient has had a contact with a hospital, suggesting that having a diagnosis is associated with a more severe depression. The same rationale can be applied to the number of psychiatric hospital/outpatient visits. These markers are to some extent proxies for depression severity, but they are not true markers of depression severity. Some residual confounding is likely.

When calculating exposure using days' supply, no associations with increased risk across comparator groups were found. The reason for this lack of association could be the increased number of false positive exposed subjects in each exposure cohort. Misclassifying women as exposed based on the day's supply evaluation could lead to an attenuation of an association between the drug and the analyzed outcome.

In the last sensitivity analysis, the cohort comprised solely of women with their first pregnancy in the study period. An increased risk of approximately 40% was observed across all comparator groups, although some were not statistically significant. In general, it has been shown that women pregnant for the first time tent to have greater pregnancy-specific distress than women pregnant after one or more viable pregnancies. (148) This distress might be more pronounced for women exposed to duloxetine, attributable to unmeasured factors that increased the risk of spontaneous abortion such as alcohol intake,(149) smoking,(150) or poor compliance to folic acid supplementation during pregnancy. (151) Women in the present study, exposed to duloxetine, were the same age as unexposed; 28.9 and 29.1 years old respectively. Despite this, women exposed to duloxetine had a significantly lower household income and a shorter education (See supplementary material Section 1.4.2.1). These factors could contribute to the assumption that women exposed to duloxetine differ in life factors that can lead to spontaneous abortions. In addition, it is not believed that there is a pharmacological explanation suggesting that women are more susceptible to duloxetine's possible side effects during their first pregnancy compared to subsequent pregnancies.

Taking the sensitivity analyses into consideration, it cannot be ruled out that there is an increased risk of spontaneous abortions for women exposed to duloxetine during pregnancy, as seen in the present study. This increased risk could be explained by factors related to the exposure (confounding by severity) due to the lack of association with women discontinuing duloxetine during pregnancy. A recent case control study based on 57,770 women from gynecological

practices in Germany study reported an increased risk of spontaneous abortions for women with psychiatric disorders (i.e. depression, anxiety, adjustment disorder, somatoform disorder) (152). This suggests that the underlying depressive disorder could be an added risk factor for women in duloxetine treatment, and that it is a challenge to discern between possible risks related to drug exposure and risks related to the underlying morbidity.

Therefore, it is recommended that women and physicians considering duloxetine treatment during pregnancy to weigh possible risks and benefits of the treatment before initiation.

To the authors' knowledge, there are no studies dealing with the association between exposure to duloxetine and elective abortions. The present study shows an increased risk compared to non-exposed, SSRI exposed, and discontinuers, but not venlafaxine exposed. The same trend is seen in the sensitivity analyses. The interpretation of these results is challenging due to the many factors leading to the mother (and father) choosing an elective abortion. One reason for choosing an elective abortion might be health issues related to the fetus, which could have been caused by, in this case, duloxetine. Since exposure to venlafaxine gives the same increased risk as duloxetine, the effects could be drug-class related. Both venlafaxine and duloxetine are second line treatments after SSRIs,(153) and the increased risk for both SNRIs compared to SSRIs could be due to women receiving SNRIs being more severely depressed which could lead to increase wish for an abortion when pregnancy is acknowledged. Other explanations could be maternal health, economic, ethics, environmental, cultural or social factors. The answer is probably not found in one factor, but in a combination of complex an interrelated reasons. (154) The rate of elective abortions was 15.1% (see Section 10.5.5) in the general population and 33.5% among duloxetine exposed. Interestingly the rate is 23.3% for those stopping duloxetine prior to pregnancy (discontinuers). This indicates that some of the increased risk is not related to duloxetine exposure, but factors (unmeasured confounders) related to being in treatment with duloxetine. Still, an association cannot be ruled out.

When interpreting the results, it is important to consider the time when the pregnancy terminations occurred. For the duloxetine exposed cohort, the median pregnancy length before the elective abortion was 55.5 days and 55.0 for duloxetine discontinuers (corresponds to approximately 7-8 weeks of gestation). For the remaining comparison groups the median length was 56.0 days. Although these differences are statistically significant, the absolute differences, of 0.5-1.0 days, are small and believed not be clinically significant. The early time of elective abortion could indicate that it is less likely due to malformations, which in general are acknowledged later in pregnancy.

The methodology in the present study is not designed to address the outcome of elective abortion in full and all the needed information is not present in the available registers.

Stillbirths was not associated with duloxetine exposure in both the main and sensitivity analyses. It is important to note that the analyses of stillbirth are limited by few cases (n=5) in the group exposed to duloxetine. There is no previous available literature analyzing this outcome specifically for duloxetine exposed. A Swedish study reported no increased risk for women

exposed to an SNRI or NRI, RR 1.7 (95% CI 0.6–3.6). (155) It is of note that the estimate is based on only 6 events.

SGA was not associated with duloxetine exposure both in the main and sensitivity analyses. In the available literature, this outcome has not previously been reported specifically for duloxetine. The analyses of SGA were performed for women exposed early and late in pregnancy, and those ending with and without a malformation. Due to the substantial number of cases, it can be concluded that there is no increased risk of this outcome. This is in line with a recent study based on Swedish data showing no increased risk of SGA for women exposed to any antidepressant. (156) No estimates for duloxetine exposed were presented.

Preterm birth was associated with a 30% increased risk compared to non-exposed and 20% to SSRI exposed, for duloxetine exposed in early and late pregnancy. Early exposure was, however, not associated with an increased risk compared to venlafaxine exposed and discontinuers which could indicate that the increased risk was confounded by the indication for an SNRI. As previously mentioned, women exposed to SNRIs could be more severely depressed, leading to unaccounted factors causing a preterm birth. However, the same argument cannot fully explain the increased risk observed for women exposed to duloxetine in late pregnancy, since the present study, in addition to non-exposed and SSRI exposed, found an almost doubling of risk compared to duloxetine discontinuers. It is known that approximately 50% of women discontinue antidepressant treatment during pregnancy (9). The reasons for being exposed throughout the pregnancy might be related to the severity of the depression. Women exposed in late pregnancy might therefore suffer from severe depression which could be related to maternal factors leading to preterm birth, and therefore differ from the group of duloxetine discontinuers. The background characteristics (supplementary material Section 1.1.5.8) for these two groups are, however, comparable on all covariates except age, income and education. These possible confounders are further adjusted for in the PS-matched analyses, which still shows an increased risk. The elevated risk seen in the analyses of late exposure period can also be interpret as a risk associated with cumulative exposure. Women exposed in the second half of the pregnancy (the late exposure period) are a subgroup of the women exposed early and therefore exposed for a longer period of time. Hence, their cumulative exposure to antidepressant medication is higher which could be the reason for the increased risk of preterm birth.

This association has not previously been described for duloxetine, but the majority of studies including this outcome for women exposed to antidepressants show an increased risk in the magnitude found in the present study. (157) Duloxetine is in the same antidepressant group as venlafaxine, another SNRI. Analyzing the risk of preterm birth for venlafaxine, two studies based on the Swedish Medical Birth Registry found similar results as the present study, with an increased adjusted OR of 1.98 (95% CI 1.49-2.63) (158) and OR 1.60 (95% CI 1.19-2.15). (155) A recent study from the UK found an adjusted OR of 1.51 (0.98-2.27) for preterm birth when comparing venlafaxine exposed to antidepressant unexposed. Although not statistically significant, the risk estimate is comparable to what is observed in the present study. (159) This suggests that the increased risk found in the present study could be explained by a SNRI class effect. An increased risk of preterm birth has also been found for women with depressive

disorders during pregnancy, who where not exposed to any antidepressant.(160) This strengthens the possibility that the increased risk for preterm birth among women exposed to duloxetine might be confounded by their depression disorder.

For the interpretation of risk of preterm birth it should be noted, that the median duration of pregnancy differed with only two days ranging from 247 to 249 days across comparison groups (Table 10.4) and most preterm births occurred in week 33 to 36 across early and late exposure, full cohorts or PS matched (Table 10.5, Table 10.6, Table 10.7, Table 10.8). Although the relative risk is statistically significant, the absolute differences of pregnancy duration are small and probably not clinically significant.

11.4. Generalizability

The findings from the present study should be generalizable as the limitations in the study are not expected to affect the biologic relations studied. However, it is important to acknowledge that selection of the comparable cohort may influence the internal validity of the study. The premise of generalizability depends therefore on a well-designed comparable cohort. This study has strived to address many possible biases related to the scientific question, within the methodological approach chosen.

It is believed that the results have a high external validity in a Nordic country setting. All pregnancies from two Nordic countries have been analyzed using highly validated and complete national registers. The authours are confident that the results are applicable to other western European countries with free and universal healthcare, since treatment regimens are comparable.

Treatment regimens are also comparable to the U.S. where indications and treatment guidelines are similar to the studied population. It is not believed that the characteristics of women using duloxetine during pregnancy differ substantially between the Nordic countries and the U.S., and therefore the results might be applicable in a U.S. setting as well.

Women excluded from the study were mostly based on limited missing data and were most probably random and not associated to exposure or outcomes.

Taking the mentioned limitations into consideration, the results can be considered to have high generalizability.

12. Other information

Not applicable.

13. Conclusions

Based on this observational register based nationwide study with data from Denmark and Sweden, no increased risk of congenital major or minor malformations was found for women exposed to duloxetine during the first trimester. Furthermore, no increased risk of stillbirths or SGA births was found.

An increased risk of spontaneous abortions was found, but data was inconclusive.

An increased risk associated with elective abortions was found. The available registers do not allow for addressing this outcome fully, and a true association cannot be ruled out, although the results suggest some degree of confounding by indication.

The increased risk of preterm birth compared to unexposed, SSRI exposed and duloxetine discontinuers is in accordance with previous studies analyzing other antidepressants. In the present study, an increased risk compared to SSRI exposed, but not venlafaxine exposed was found, suggesting an SNRI class effect. Furthermore, the absolute difference in pregnancy duration did not differ much.

Women and physicians considering duloxetine treatment during pregnancy are therefore to weigh possible benefits for the mother against risks for the unborn child for each individual case.

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Annex 1. List of standalone documents

No.	Document Reference No	Date	Title
1.	1	September 2019	Supplementary material

Annex 2. Additional information

Not applicable.